THEORETICAL ASPECTS OF THIOAMIDES.

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ABSTRACT:
Quantum chemical calculations can afford valuable information to understand the chemical processes and the structural features of chemical species. This tool has become very informative and several aspects can be discussed on the thioamides under a theoretical point of view such as the effects of structure in their planarity and some cases with derivations of that planarity, C-N bond rotation in comparison to the related amides and selenoamides and implications in the transition state, and the influence of the solvent or the influence of remote substituents. This review will deal as well with isomerization processes such as tautomerization or rotation of *N*-bonded methyl groups. Some aspects of reactivity of thioamides such as the Bond Dissociation Enthalpy (BDE) or their behavior as radical scavengers are discussed as well. Some comments on the theoretical aspects of thiopeptides are briefly analyzed.

KEYWORDS:
THIOAMIDES, QUANTUM CHEMISTRY, DFT, HF

1. BASIC STRUCTURAL FEATURES OF THIOAMIDES.

1.1 Planarity of thioamides.

The planarity of thioamides has been a deeply explored subject not only from a theoretical point of view but also from the multiple implications it might have in life science or materials. In this review we will cover the thioamides under a theoretical point of view focused on the effects of structure in their planarity and the consequences on their behavior. Judge et al. studied the structure of thioformamide at the HF/3-21G* level finding that the lower energy state is strictly planar (structures **1** in Figure 1. 1).[1] High level theoretical calculations performed by Kowal confirm the planar geometry of the thioformamide $H_2NC(S)H$.[2] In the same work it is described that Correlation-Corrected Vibrational Self-Consistent Field (CC-VSCF) affords a good description of the vibrational features of the thioamide group.

Hambley et al.[3] have shown how the optimized structure (BLYP/6-311++G**) of thioacetamide is in good agreement with its crystal structure. The thioacetamide shows a planar structure in which there is conjugation in the S-C bond but little hyper-conjugation in the C-N bond. These results indicate that the canonical form (**1a**) shown in Figure 1. 1 predominates in the solid state.

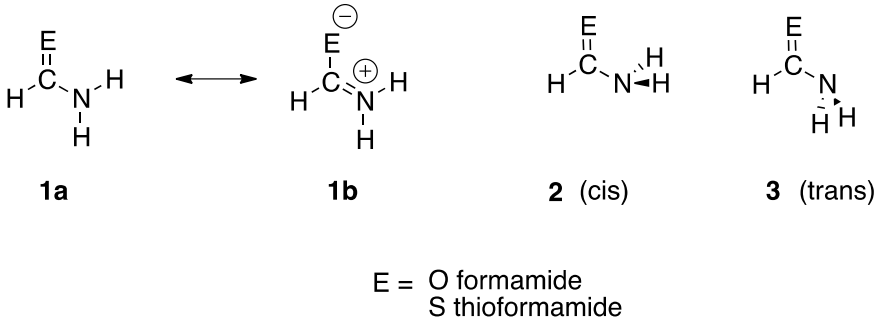


Figure 1. 1 Resonance forms of the amides and thioamides (**1a** and **1b**) and transition states (**2** and **3**) in the rotation around the C-N bond

More complicated thioamides such as ethyl 2-{[(*Z*)3-(4-chlorophenyl)-3-hydroxy-2-propene-1-thione]amino}acetate (Figure 1. 2) studied at the levels of theory HF/6-31G(d) and B3LYP/6-31G(d), display a planar geometry on the thioamide unit in good agreement with the crystallographic characterization.[4]

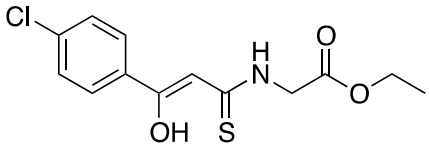


Figure 1. 2 Estructure of ethyl 2-{[(Z)3-(4-chlorophenyl)-3-hydroxy-2-propene-1-thione]amino}acetate

1.2 Derivations from planarity.

Despite the trend of thioamides to adopt a planar geometry, the electronic nature on the substituents of the thiocarbonyl group can determine the planarity of the thioamide, as shown by Hori et al.[5] They found that in a series of *para*-substituted or unsubstituted thioaroyl-7-azabicyclo[2.2.1]heptanes the planarity of the thioamide can be tuned by altering the electronic nature of the substituent.

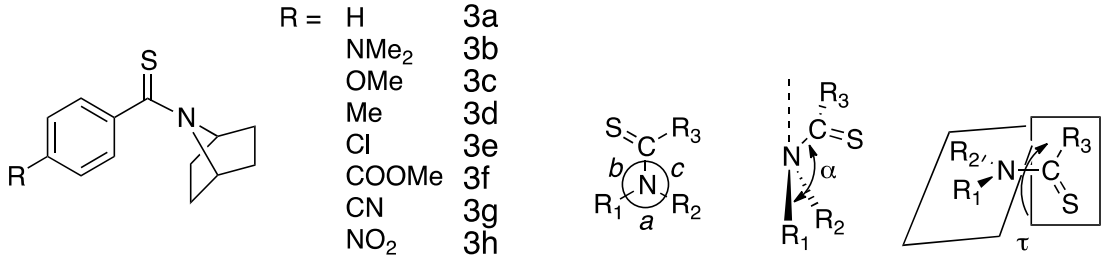


Figure 1. 3 Thioamides studied by Hori et al. and definition of angle parameters. Adapted from reference [5]. Copyright 2008 American Chemical Society.

For example, the H-substituted compound was substantially both nitrogen-pyramidal and twisted (**3a**, α=167.3° and $|\tau|$ = 11.0°), while in the *p*-nitro-substituted compound, planarity was substantially restored (**3h**, α=175.2° and $|\tau|$ = 0.1°). The planarity of thioamide nitrogen can be represented in terms of three angle parameters, θ, α and τ, the definitions of which are shown in Figure 1. 3: θ is the sum of the three valence angles

around the nitrogen atom ($\theta = a + b + c$); the hinge angle α is the angle between the N-C(S) bond and the plane defined by the nitrogen atom, R_1, and R_2; and the twist angle $|\tau|$ is the absolute value of the mean of two torsion angles, $\omega_1(R_3CNR_2)$ and $\omega_2(SCNR_1)$ ($|\tau| = 1/2|\omega_1+\omega_2|$).[6] Values of θ, α, and τ of the ideal planar thioamide are 360°, 180°, and 0°, respectively. The former two values will decrease and the third value will increase as the thioamide functionality deviates from planarity to a greater extent.

In the solid state, an electronic effect of the aromatic substituent (R) on thioamide planarity was clear in the case of the bicyclic thioamides (not observed on analogous amides), and the degree of planarity represented in terms of R is in the order **3h** > **3e** > **3a** > **3d** > **3b**. The thioamide **3h** (R = NO_2) takes a nearly planar structure, whereas **3b** (R = NMe_2) takes a significantly nitrogen-pyramidalized structure (Figure 2 on the reference [5]). This trend is consistent with the idea that an electron-withdrawing group tends to restore nitrogen planarity, except for **3f** (R = COOMe) on which packing effects induce a distortion. To estimate the N-C(S) double bond character of these thioamides in solution, rotational barriers with respect to the thioamide bond were evaluated by variable-temperature ^{1}H NMR spectroscopy. It is observed that the substituent on the benzene ring showed a significant electronic effect on the rotational barrier of the thioamides (a wide discussion on rotational barriers in thioamides will be found bellow in the section 3). A more electron-withdrawing group tends to increase the rotational barriers of these thioamides.

These experimental facts were modeled with DFT calculations at the B3LYP/6-311+G(d,p)// B3LYP/6-31G(d) level of theory. For the punctual calculations solvent effects were taken into account using the PCM model and a relative permittivity ε = 35.6 to simulate nitrobenzene. There is a tendency that the degrees of nitrogen-pyramidalization of the calculated structures are consistently larger than those of the solid-state structures. Also, the calculated rotational barriers of these thioamides showed that the rotational barriers of the bicyclic thioamides are consistently smaller than those of the monocyclic thioamides displaying a good linear relationship with the Hammet parameter σ_p^+ values of the substituents.[7]

To explain these observations, it is needed a scheme of resonance including a new structure (Figure 1. 4).

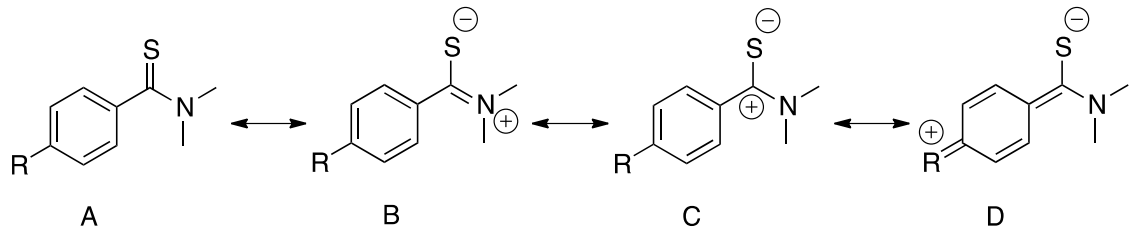


Figure 1. 4 Resonance forms including the effect of the substituents on the *para*-substituted thioaroyl group. Adapted from reference [5]. Copyright 2008 American Chemical Society.

The results obtained by Hori et al. are consistent with the idea that the relative contributions from resonance B versus resonance D (Figure 1. 4) control the planarity of the nitrogen. Only resonance B requires the nitrogen to be planar (pyramidalization and twisting will destabilize the C=N bond). Strongly electron-withdrawing substituents (R)

at the *para* position destabilize resonance D (increasing A and B), thereby increasing planarity.

In the same work, the authors have found that tying the nitrogen into a bicyclic structure pyramidalizes nitrogen and decreases the contribution from resonance B (increasing A and D) in comparison with thioamides with the nitrogen atom belonging to a pyrrolidine monocyclic structure.

Kesharwani et al.[8] have studied the theoretical possibility to stabilize the nonplanar forms of thioamides when compared with their planar structures.

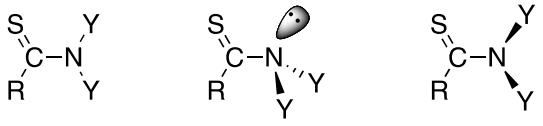


Figure 1. 5 Thioamides studied by Kesharwani et al.[8]

In the models studied twist and pyramidal forms are more stable than planar form. The destabilization caused in the planar form of *N*,*N*-difluorothioformamide is due to the repulsion between the lone-pairs of the C=S sulfur atom and the *N*-substituted fluorine atom.[8] Negative hyperconjugative type interactions, in addition to the electrostatic effect, are proposed to be responsible to the stabilization of the twisted conformation because second order perturbative (NBO[9,10]) analysis suggests that the negative hyperconjugative type interactions ($n_N \rightarrow \sigma^*_{C\text{-}F}$) in the twisted form with substituents R = F, Y = F (Figure 1. 5) is stronger by 3.2 kcal/mol than that with substituents R = H and Y = F ($n_N \rightarrow \sigma^*_{C\text{-}H}$) at B3LYP/aug-cc-pVDZ level.[11] Nevertheless, the fact that in some cases the twisted form has not been found indicates that electrostatic repulsions override these interactions.

Thioamides with three-membered azirine and aziridine rings have been studied as well in the same work,[8] finding that only the azirine rings stabilized the twisted form with substituents R = H and Y = CH=CH when compared with the prototype planar structure. The aziridine derivatives do not show twisted form and in all cases the pyramidal form is the most stable structure. The hybrid approach using a combination of explicit solvent molecules and continuum model shows that the twisted form of thioamide derivatives would be much more favored due to the hydrogen bonding interaction with solvent molecules.

2. TAUTOMERIZATION.

One of the simplest analyses that can be proposed for thioamides is the tautomeric equilibrium shown in Figure 1. 6.

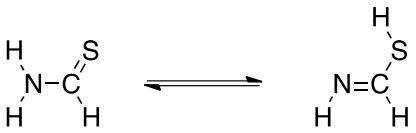
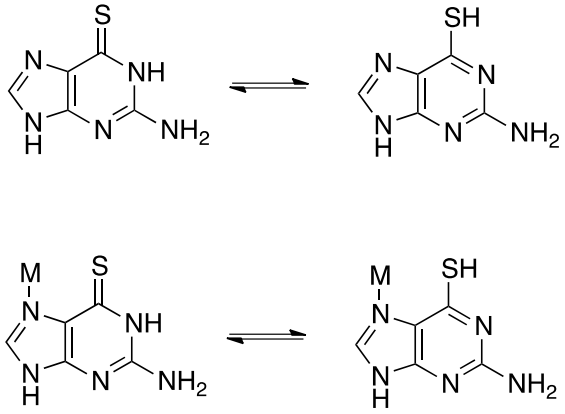


Figure 1. 6 Tautomeric equilibrium in thioamides.

Quantum chemical calculations have been carried out to evaluate the relative energies of both tautomers by Leszczynski et al.[12] Hartree-Fock and post-Hartree-Fock calculations show that the thioamide form is about 10 kcal/mol more stable than the acidic form (thiol form, structure on the right side in Figure 1. 6).

Zhang et al. have studied this kind of intramolecular proton transfer in the 6-thioguanine (a drug with cytotoxic and immunosuppressive properties) and the influence of alkali metals cations in the equilibrium at the level of theory B3LYP/6-31+G(d).[13]



M = Li^+, Na^+, K^+

Figure 1. 7 Tautomeric forms of 6-thioguanine in the absence of the alkali metal (above) and in the presence of the metal (below).

Although the 6-thioguanine is capable of existing in fourteen tautomeric forms the work of Zhang et al. focuses on the intramolecular proton transfer shown in Figure 1. 7. Despite the amide form is more stable in the simplest thioamide studied by Leszczynski et al.,[12] in the more complex system of 6-thioguanine at the level of theory B3LYP/6-31+G(d), it is found to be more stable the thiol form by 1.9 kcal/mol. When the alkali cations are present, the amide form is more stable by 17.0, 15.4 and 11.7 kcal/mol for Li^+, Na^+ and K^+ respectively. The comparison of the calculated barriers indicates that the presence of the cations increases the activation barrier for the proton transfer. And considering only the systems with alkali metals present, the greater the radius of the alkali metal cations, the easier the intramolecular proton transfer in 6-thioguanine.

3. ROTATIONS AROUND THE C-N AMIDE BOND.

3.1 Simple examples:

The dynamic modification that has been most studied both experimentally and theoretically is the **rotation around the C-N amide bond**. Several of these studies have been performed in comparison with the analogous amides and selenoamides.

At first sight, as the difference in electronegativity between C and S is small,[14] the C=S bond should not be strongly polarized as it is in the C=O of formamide, indicating that the resonance form **1b** (Figure 1. 1) should have more importance in amides than in thioamides. The C-N bond should display a higher character of double bond in formamide than in thioformamide and a higher rotational barrier for formamide should be expected. Nevertheless, the energy value for rotational barrier in thioformamide is larger than for formamide.[15,16]

Ferrettti et al. have studied the deformation of the fragment $R(X=)C\text{-}NR_2$ present in amides, thioamides, amidines, enamines and anilines by a combination of the analysis of crystal structures and *ab initio* calculations HF/4-31G.[16] The authors find that the thioamides have a higher rotational barrier than amides.

Wiberg and Rablen had studied the rotational barrier at MP2/6-31+G* and G2 levels of theory to rationalize the higher rotational barrier of thioamide (see values in Table 1. 1).[15] The change in the charge density on the rotating the amino group in formamide and thioformamide has been examined finding that there is a bigger net charge change in the sulfur atom of the thioformamide (a net change of 0.116e) than in the oxygen atom of the formamide (0.057e). The bigger change on the values of charge found on rotating about the C-N bond indicates that thioformamide is closer to the representation of the resonance picture **1a** and **1b** shown in Figure 1. 1 than the formamide.

The authors of this work propose that there is a considerable transfer of π charge to the sulfur in the planar form. To justify the important charge transfer from N to S in thioamides (and not very important from N to O in amides) it is possible to propose two important factors. Initially, the sulfur atom in the C=S bond has a relatively small charge whereas the oxygen of the C=O group has a relatively large negative charge, and consequently, the energetic cost of further polarization is quite large. A second factor is the size of the sulfur atom. The larger size of the sulfur makes it able to accommodate additional charge transfer. Therefore, it is important to keep in mind that charge transfer is a factor that contributes to the barrier. This higher barrier is in accord with a higher wave number of the NH_2 out-of-plane wagging mode in gaseous thioformamide than in formamide. Calculation of the NH_2 wagging mode potential in formamide and thioformamide on the G2 level revealed that the potential is steeper in the case of thioformamide, leading to the conclusion that the thioformamide molecule is less floppy than its oxygen analog.

Table 1. 1 Energy of rotational barriers of formamide and thioformamide [15]

Rotational Barriers, kcal/mol[a]		
Compound	MP2/6-31+G*	G2
Formamide	17.2	16.0
Thioformamide	18.8	18.0
Formic acid	12.9	11.5
Thioformic acid	12.9	12.3

[a]The values include the change in zero-point energy.

Ou et al.[17] performed NBO calculations[9,10] at the levels of theory HF/6-31G**, MP2/6-31** and MP4/6-31** founding that the rotational barrier height of

thioformamide relative to formamide is due to the more important contribution from the zwitterionic structure **1b** (Figure 1. 1) in the former, in a similar description than the description of Wiberg and Rablen.[15] The zwitterionic structure strengthens the C-N bond with double bond character and thus inhibits the C-N rotation.

Laidig and Cameron proposed that the higher barrier observed in the rotation of thioformamide when compared to the formamide is difficult to explain with a simple resonance model.[18] These authors rationalize that the higher electronegativity of O attracts charge to itself, shortening the C-N bond length and increasing the bond order (hindering rotation). In thioformamides the O atom is replaced by a less electronegative S atom. Although the S atom is more polarizable than O and could better stabilize a negative charge, it is not sufficient electronegative to pull charge from the N atom, making difficult to understand the higher rotational barrier found in thioformamide. In this different approach the authors consider that in the C-N rotation process there is a pyramidalization of the nitrogen atom and the dominant change is the interaction between the C and N atoms, with much smaller changes in the interaction between C and S, or C and O in formamide. For these authors, there is no significant delocalization of electronic charge between the N and S atoms in planar thioformamide or between N and O in formamide.

The planar conformation (structures **1a** and **1b** in Figure 1. 1) is the lowest energy structure (as described previously[1,2]), with the cis and trans structures (**2** and **3** in Figure 1. 1) transitions states 19.9 and 21.6 $kcal \cdot mol^{-1}$ less stable. The energetic changes are consistent with bond lengthening processes in which the loss in attraction between the bonded fragments outstrips any decrease in repulsion as the atoms move away from one another. The largest geometric change in bond length upon rotation on the amide bond is the lengthening of the C-N bond, while the other bond lengths show very small changes and the energetics are dominated by the lengthening of the C-N bond. As the NH_2 fragment rotates away from planarity, the nitrogen pyramidalizes and charge is transferred from N to its bonded neighbors, C and H. The interaction between C and S (or C and O in formamide) is relatively unchanged, with only a small transfer of charge from S to C and small change in bond length. The energetics is dominated by the lengthening of the C-N bond and the resulting loss in intra and inter-atomic stabilization of N. The driving force for the planarization of N is the stabilization of N through its increased electronegativity (more *s* character in sp^2 hybridization than in sp^3) and subsequent withdrawal of charge from its bonded neighbors. Under the point of view of Laidig and Cameron, thioformamide can be considered as a 'thioformyl-amine'. The thioformyl group behaves merely as a substituent on an amine, and the barriers to rotations are special cases of a barrier to inversion of the corresponding amines. As the planar sp^2 N pyramidalizes, its hybridization shifts toward sp^3, the result of which is that N becomes effectively less electronegative and submits electronic charge to its bonded neighbors. Considering the difference between amides and thioamides, the softer thioformyl group donates more charge to the NH_2 group than does the more polarized formyl group in the planar conformation. Thus, rotating about the C-N bond, which leads to the rehybridization of the N and its pyramidalization, is more costly for the N atom and the NH_2 group in thioformamide.

Laidig and Cameron find in their work that the structure **2** of Figure 1. 1 is more accessible than the structure **3**. Interestingly, Lim and Francl[19] using the level of

theory HF/3-31G found that the structure **3** was lower in energy than the structure **2** for thioformamide and thioacetamide.

The point of view of Laidig and Cameron has been used by Choe et al.[20] to explain the higher C-N bond rotational barrier of thioacetamide in comparison with acetamide at the MP2/6-31G** and B3LYP/6-31G** levels of theory. They carried out a NBO population analysis finding that the lone pair electrons on the nitrogen of acetamide has more *s* character than that of thioacetamide in transition state ($sp^{2.40}$ versus $sp^{2.28}$ respectively). The relatively large *s* character of lone pair electrons of acetamide nitrogen in its transition state reduced the orbital energy, leading to the lower rotational barrier.

Lauvergnat and Hiberty have checked the validity of the resonance representation by means of an *ab initio* valence-bond study.[21] The authors of this work studied the problem by a method that allows to directly measure the stabilization brought by the delocalization of the nitrogen lone pair in planar (thio)amide, by comparing the energy of the fully delocalized ground state to that of an adiabatic state in which the lone pair is constrained to remain strictly localized on the nitrogen atom. Doing this for both the planar and the twisted forms allows the contribution of resonance to the rotational barrier and, more generally, to the properties associated to the special stability of the planar form to be estimated.

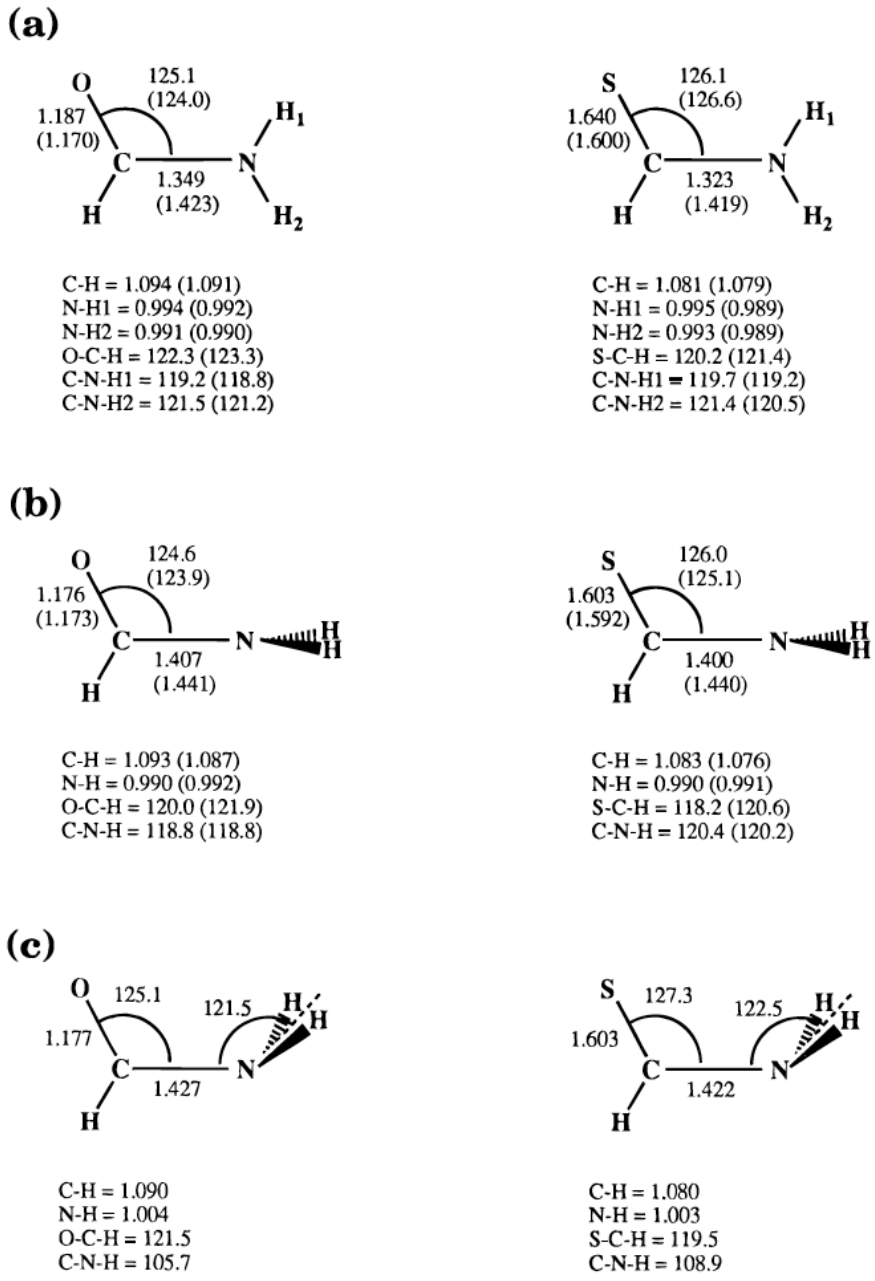


Figure 1. 8 Geometries of the delocalized states and, in parentheses, of the localized states of formamide and thioformamide: (a) planar conformers, referred to as sp^2-90º; (b) sp^2-90º-rotated conformers, and (c) sp^3-90º-rotated conformers [21]

In their study the authors have compared structures with planar (thio)formamide, 90º rotated (thio)formamide keeping sp^2 hybridization on N (referred as sp^2-90º, see Figure 1. 8) and 90º rotated (thio)formamide changing to sp^3 hybridization on N atom (referred as sp^3-90º, see Figure 1. 8). The first point the authors highlight is the shorter C-N distance in the conformer sp^2-90º than in the sp^3-90º, indicating that the C-N lengthening upon rotation is not entirely due to loss of conjugation but partly arises from a change of hybridization at the nitrogen atom, as sp^3 hybrids are generally known to form longer bonds than sp^2. The authors found, as well, little differences between the C-O, C-S and C-N bond lengths of the planar conformers in their lone-pair localized diabatic states (i.e. with the nitrogen lone pair localized on the nitrogen atom) and those

of the pyramidal-twisted conformers in their ground states (sp^3-90º), supporting the idea that the rotation around the C-N bond is mainly a matter of localization-delocalization. The analysis of the structural values showed a significant C=S shortening accompanying loss of conjugation in thioformamide (0.040 Å) suggesting the two-structure resonance model picture as an adequate representation for thioformamide (Figure 1. 1). In addition, the comparison of structures with and without delocalization suggests that the C-N linkage has more double bond character in thioformamide than in formamide, accounting for a higher rotational barrier.

The analysis of the energies of these structures allowed to have directly measured the stabilization that delocalization of the lone pairs of the nitrogen atom brings to planar conformations and 90º-rotated conformations, and the contribution of this resonance stabilization to the rotational barrier around the C-N bond, finding that conjugation of the π electrons is an important feature of the electronic structure of (thio)amides with the lone pair of the nitrogen atom significantly delocalized over the (thio)carbonyl group. The authors estimate a more important conjugation in thioamides than in amides. Nevertheless, the resonance stabilization to the C-N rotational barrier is not the only one factor accounting for this energy, suggesting tentatively the preference of the lone pair of the nitrogen atom for a direction perpendicular to the molecular plane, following the minimum of electron density at the carbon atom as an additional factor to this rotational barrier. Finally, despite this additional factor affecting the C-N rotational barrier, the authors indicate that the larger barrier of thioamides is due to a greater importance of conjugation effects relative to amides.

A new study with Valence Bond resonance model for derivatives of formamide $HCX(NH_2)$, where X = O, NH, CH_2, S and Se, using the block-localized wave method (BLW)[22–24] was carried out by Mo et al.[25]

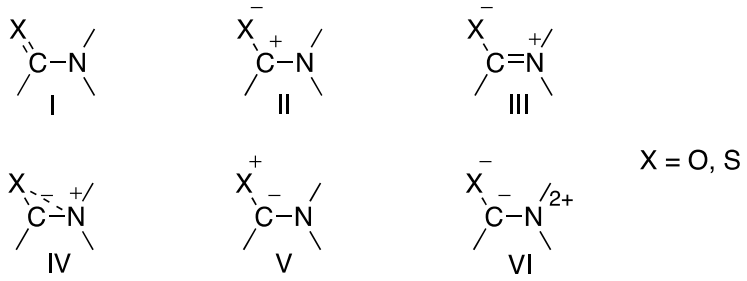


Figure 1. 9 Six resonance structures resulting from four π electrons and three π-type atomic orbitals according to Valence Bond Theory in amides and thioamides

The rotational barriers of $HCX(NH_2)$ are decomposed into various energy components, including resonance conjugation energy, σ-framework steric effects, hyperconjugation energy, and pyramidization energy, using a BLW function method with the 6-31G(d) basis set. The ground-state electronic delocalization, represented by resonance structure **III** of the Figure 1. 9, makes the largest contribution to the torsional barrier about the C-N bond, though the gain in hyperconjugation stabilization of a structure with the NH_2 fragment rotated 90° reduces the overall delocalization effects. Steric effects due to conformational change in the σ-framework and amino group pyramidization are also important in determining the barrier height of these compounds. The difference in torsional barrier in the chalcogen series, $HCXNH_2$ (X = O, S, and Se), primarily results from the difference in electronic delocalization of the ground-state structure, which is

significantly greater for X = S and Se (-35.7 and -37.6 kcal/mol respectively) than X = O (-25.5 kcal/mol).

An additional work validating the resonance representation of the formamide and its chalcogen replacement analogues (thioformamide among them) was presented by Glendening and Hrabal.[26] These authors study the influence of resonance on the structure and rotational barrier of formamide and its S, Se and Te replacements analogues using the natural bond orbital methods, NPA[27] and NRT.[28–30] This study suggested that the weight of the dipolar form **1b** (Figure 1. 1) increases from formamide to telluroformamide in good agreement with the increase of the C-N rotational barrier.

The authors find the same structural features described previously upon rotation around the C-N bond (more significant changes for the C-N bond than for the C-S). The elongation of the C-N bond is due to two contributions, one of them is the rehybridization of the nitrogen atom (about one third) and the other contribution is delocalizing effect (about two thirds, treated by resonance theory). The analysis of influence of rotation on the natural charges of NPA shows stronger charge transfer for the heavier chalcogens from the nitrogen atom to the chalcogen atom, and rotation from non-planar to planar geometry is principally accompanied by charge transfer from N to the chalcogen. It can be surprising that the less electronegative elements can accommodate more formal negative charge (increasing the contribution of the form **1b** Figure 1. 1), nevertheless, the larger polarizability of the heavier elements explains this fact[15,18] and it is in good agreement with increased rotational barriers and decreased C-N bond lengths (i.e. more participation of the form **1b** of Figure 1. 1) for the heavier chalcogen derivatives. Nevertheless, a similar analysis of the variation of charges upon rotation using AIM theory[31] gives a different charge transfer that do not matches with the conventional resonance theory (in AIM theory the authors find that rotation from non-planar to planar geometry is principally accompanied by charge transfer from C to the S and N atoms in an almost identical amount - figure 3 in the article[26]). The authors conclude that atomic charges cannot be uniquely defined, so neither NPA nor AIM should be considered to give the ‘‘correct’’ charges and they focus the solution of the problem through Natural Resonance Theory (NRT). This theory explains the planar structure as hybrid of resonance with two principal structures (**1a** and **1b** in Figure 1. 1). The structure **1b** has a higher relative weight in thioformamide than in formamide. As a result, C-N double-bond character is higher in thioformamide than in formamide, accounting for a higher C-N rotational barrier.

The amide and thioamide has been used to present a two-state model based on the BLW method on which no empirical parameter is required (BLW-DFT).[32] The results of the structural changes indicate higher resonance energies in thioformamide than in formamide. These calculations provide contributions of the resonance structures shown in Figure 1. 1, giving values of 72% and 28% for structures **1a** and **1b** respectively in amide and values of 58% and 42% in thioformamide, in accordance with its high resonance energy as compared to formamide.

Barantham et al.[33] have performed a comparative study of the C-N bond rotational barriers of amide, thioamide and selenoamide at the HF/6-31G* and MP2/6-31G* levels of theory. The analysis of the variation of the C-N bond length shows that this value decreases in the order amide > thioamide > selenoamide, indicating that the C-N bond

order is increasing when moving from O to Se. The difference of the values of this length in planar and rotated structure (structure **2** of Figure 1. 1) increases from O to Se, indicating that the thioamide has a C=N double bond character that is intermediate to amide and selenoamide. The calculated rotational barriers show the same trend, being the barrier of the thioamide an intermediate value between the amide and selenoamide barriers. The variation of NPA charges, evolving from the structure **2** of Figure 1. 1 to the planar structure, show the increase in the charge of X and the decrease in the charges of NH_2. The charge flow from the NH_2 group to X increases in the order amide < thioamide < selenoamide. These results support the delocalization of the nitrogen lone pair onto the π framework as suggested by the resonance model, especially for thioamide and selenoamide. However, the electronegativity does not seem to be the driving force of the electronic delocalization.

The NBO theory[9,10] has been used by Kim et al.[34] to explain the nature of rotational barriers of the C-N bond in amides, thioamides, ureas and thioureas, on the basis of barrier-forming N(lp)/C-O(π)* interaction and the antibarrier-forming N(lp)/C-O(σ)* interactions. Kim et al. found that the N(lp)/C-S(π)* interaction in thioamide is stronger than the N(lp)/C-O(π)* interaction in amide.

Using as well NBO theory[9,10] Bharantham et al.[35] have performed a comparative study of the rotation around the C-N bond in amides, thioamides and selenoamides (X=C(H)-NH_2 where X = O, Se or Se). The C-N rotational barriers obtained at the G2 level are in the order 15.97 < 18.02 < 19.72 kcal/mol respectively. The calculated C-N rotational barriers in these systems account for two factors: (1) the energy rise due to breaking the partial pπ-pπ bond between carbon and nitrogen and (2) the energy gain due to the $n_N \rightarrow \sigma^*_{C\text{-}X}$ negative hyperconjugation in the rotational transition state. NBO calculations show that the $n_N \rightarrow \pi^*_{C\text{-}Se}$ delocalization is very strong with a second-order interaction energy ~120.4 kcal/mol (the second order delocalization energies $E^{(2)} = F_{ij}/2\Delta E_{ij}$ are quantitative and representative of the extend of lone pair delocalization, where $E_{ij} = E_i - E_j$ is energy difference between the interaction of molecular orbitals *i* and *j* and F_{ij} is the Fock matrix element for the interaction between *i* and *j*). This strong delocalization is due to the small energy difference ΔE (0.45 au) and strong F_{ij} (0.208) between the interacting orbitals. The partial pπ-pπ C-N bond strength increases in the order formamide < tioformamide < selenoformamide because the N lone pair delocalization in these systems follows the same order (Table 1. 2). This is evidenced by the decrease in electron density on the nitrogen lone pair in formamide (1.802), thioformamide (1.740) and selenoformamide (1.723) and the increase in the second-order energy $E^{(2)}$ due to bond delocalization in formamide (89.05 kcal/mol), thioformamide (111.2 kcal/mol) and selenoformamide (120.4 kcal/mol).

Table 1. 2 NBO Analysis of formamide (f), thioformamide (tf), and selenoformamide (sf) at the MP2(full)/6-31+G* level

		second-order interaction			occupancy		charges			
compound	interaction	$E^{(2)}$ [a]	$E_i - E_j$	$F_{i,j}$	$\rho_{n(N)}$	$\rho_{\pi^*(C-O)}$	X	C	H	NH_2
f-1	$n_{N3}-\pi^*_{O1-C2}$	89.05	0.59	0.205	1.802	0.192	−0.724	0.661	0.147	−0.083
f-2	$n_{N3}-\sigma^*_{O1-C2}$	14.45	1.41	0.128	1.970	0.030	−0.633	0.658	0.158	−0.183
f-3	$n_{N3}-\sigma^*_{O1-C2}$	7.36	1.41	0.091	1.969	0.031	−0.599	0.943	0.137	−0.180
tf-1	$n_{N3}-\pi^*_{S1-C2}$	111.2	0.47	0.205	1.740	0.252	−0.204	−0.002	0.223	−0.007
tf-2	$n_{N3}-\sigma^*_{S1-C2}$	12.14	1.07	0.102	1.968	0.034	−0.018	−0.057	0.227	−0.152
tf-3	$n_{N3}-\sigma^*_{S1-C2}$	2.24	1.07	0.053	1.973	0.035	0.037	0.089	0.208	−0.157
sf-1	$n_{N3}-\pi^*_{Se1-C2}$	120.4	0.45	0.208	1.723	0.269	−0.161	−0.059	0.228	−0.008
sf-2	$n_{N3}-\sigma^*_{Se1-C2}$	12.87	0.94	0.098	1.965	0.036	0.049	−0.127	0.230	−0.153
sf-3	$n_{N3}-\sigma^*_{Se1-C2}$	3.20	0.94	0.049	1.971	0.037	0.109	−0.163	0.213	−0.159

[a] In kcal/mol. [b] In au.

The indexes 1, 2 and 3 refer to planar, cis and trans structures respectively in Figure 1. 1.

Careful analysis of NBO data indicates that the increase in the delocalization as going down the period is mainly attributable to the decrease in the energy difference between the energies of the N lone pair and the π* orbital of C-X bond: 0.59 (formamide), 0.47 (thioformamide), and 0.45 kcal/mol (selenoformamide). On the other hand, the electronegativity of X strongly influences the $n_N \rightarrow \sigma^*_{C-X}$ negative hyperconjugative interaction. Hence, in the transition state **2** of Figure 1. 1 for formamide (entry f-2 on Table 1. 2) this interaction is much stronger than in analogous transition state for thioformamide. The increase in the pπ-pπ delocalization (in formamide < thioformamide < selenoformamide) and decrease in the anomeric π interaction (in the transition states **2** of formamide > thioformamide > selenoformamide) complement each other in increasing the C-N rotational barrier in thioformamide relative to formamide. In selenoformamide, the ΔE between the N lone pair and π^* of C-Se is small and hence the N lone pair delocalization is strong, relative to thioformamide and formamide. Moreover, as the observed delocalization order does not follow the increasing electronegativity order, it can be concluded that the electronegativity of X does not play an important role in the delocalization in these systems and the NBO analyses indicates that it is the π^* orbital who plays an important role in increasing the electron delocalization. The π^* interaction in the C=X bond in $X=CRNH_2$ mainly depends on the p orbital coefficients on X and C and the distance between the atoms. With the increase in the n value, the 2p-np antibonding overlap decreases (n is 2, 3 and 4 for O, S and Se respectively) in addition, the C=X bond length increases with the size of X, decreasing the π^* strength, which leads to a decrease of the energy of the π^* orbital and a decrease in the energy difference (ΔE) between the *N*-lone pair and the π^* C-X orbital. As ΔE decreases, charge transfer from the lone pair to the π^*orbital increases and hence the charge transfer to X increases as reported.[15,21,36]

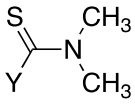
The same arguments based on conjugative $n_N \rightarrow \pi^*_{C-S}$ delocalization interactions have been used by Zukerman-Schpector et al. to explain the significant double character of the C-N bond in the energy minimum structures of *N*,*N*'-bis(pyridin-*n*-ylmethyl)ethanedithiodiamides (*n* = 2, 3 and 4).[37]

In an extension of the work of Bharantham et al.[35] the different variation of the C-N and C-X (X=O, S, Se) bonds upon rotation has been reported by Kaur et al.[11] by studying a collection of amides, thioamides and selenoamides, $H_2NC(=X)Y$, where X=Se, S, O and Y=H, F, Cl, Br, NO_2, CN, NH_2, CF_3, CH_3, SH, at the MP2/6-31+G* level of theory, in a comparative study. In this study, the authors analyzed the influence of the groups Y directly bonded to the carbon atom on the rotation around the C-N

bond. In all cases the C–N bond distance elongates and C–X bond distance (X = O, S, Se) contracts in the transition state. The variation in C–X bond distance is smaller than that in C–N bond distance, in good agreement with reported previous works.[18,21] The planar geometry is found in the ground state of most compounds, while a pyramidal character in N atom is found in the transition states (geometries **2** and **3** of Figure 1. 1). The study of variation of charges done at MP2/6-31+G* level, using MP2 densities by NBO method, focusing in the compounds with Y = H shows a parallel behavior on the nitrogen atom between thioamides and selenoamides. In both cases the nitrogen atom carries negative charge (0.82 and 0.83 units for selenoamide and thioamide respectively). The charge density on nitrogen increases by 0.15 units in both the rotational transition states (structures **2** and **3** in Figure 1. 1), which is clearly reflective of delocalization of electrons from nitrogen in the ground state that is disrupted in the transition states. In the ground state the charge of sulfur and selenium is slightly negative (-0.09 and -0.05 units respectively) and decreases by 0.18/0.22 and 0.21/0.25 units respectively in TS represented by structures **2**/**3**, while the carbonyl atom undergoes a very small change in the charge during the rotation. For comparison, formamide shows a more negative charge on oxygen (-0.72 units) than that on selenium or sulfur in seleno- and thio-formamide respectively, but the variation of this charge with C-N bond rotation is smaller than the analogous in thioamides and selenoamides (0.09/0.12 units in structures **2**/**3)**. This higher charge is attributed to the higher electronegativity of oxygen, and therefore positive charge on carbon is also increased. Interestingly, the nitrogen is more negatively charged than the same atom in thio- and seleno-formamide (-0.82 units for selenoformamide, -0.83 units for thioformamide and -0.95 units for formamide). The variation in charge on nitrogen in formamide from ground state to structures **2** and **3** is only 0.06 and 0.04 units, respectively. These values are clearly lower than the charge variations observed for thio- and seleno-amides (0.14 units for both structures in thioformamide and 0.15 units for both structures in selenoformamide), and the different substituents do not change the tendency. It can be clearly seen that charge transfer from nitrogen to chalcogen in transition states is larger in heavier chalcogens than lighter ones, because of the larger polarizability of the heavier chalcogens, that allow them to accept more charge density. These results are in good agreement with the earlier report of Wiberg and Rablen[15] and confirmed by Kaur et al.[11] The second order delocalization energy value $E^{(2)}$ for $n_N \rightarrow \pi^*_{S\text{-}C}$ delocalization in thioformamides is slightly lower to that in selenoformamides (for Y=H these values are 111.5 kcal/mol in the thioformamide and 120.4 kcal/mol in the selenoformamide, and similar trend is observed for the rest of the examples studied) which explains the higher rotational barrier in the selenoformamides relative to that in thioformamides. As said above, the higher delocalization in selenoformamide is the result of smaller energy difference between the donor and acceptor orbitals, which in turn indicates better charge acceptor capability of selenium. The $E^{(2)}$ value for $n_N \rightarrow \pi^*_{O\text{-}C}$ is further reduced in amides in comparison to substituted thio- and seleno-amides. The effect of substituents on $n_N \rightarrow \pi^*_{O\text{-}C}$ is stronger than in thio- and seleno-amides, playing a relatively more important role in stabilization of the transition states in amides than in thio- and seleno-amides. It is the $n_N \rightarrow \pi^*_{X\text{-}C}$ interaction that stabilizes the ground state and contributes mainly to the rotational barrier. The $n_N \rightarrow \sigma^*_{C\text{-}Y}$ interactions are decisive of the substituent effect in thio- and seleno-amides. These interactions tend to stabilize the transitions states thereby decreasing the rotational barrier. The C-N rotational barriers for all the substituted thio- and seleno-amides studied decrease relative to their respective thio- and seleno-formamides due to a stabilization of transition states and that decrease is more significant in halo substituted selenoamides. The NBO analysis

explains the decrease in rotational barrier as resulting from stabilization of transitions states (increase in $n_N \rightarrow \sigma^*_{C\text{-}Y}$ and $n_N \rightarrow \pi^*_{X\text{-}C}$ interactions). The presence of methyl substituents decreases the C-N rotational barrier in oxo-, thio- and seleno-amides which can be understood as the result of stabilization of the transition state. The decrease is more pronounced in the rotational barrier through a transition state represented by structure **2**.

An experimental and theoretical study performed on the *N*,*N*-dimethylthioamides shown in Figure 1. 10 has been developed by Neugebauer Crawford et al.[38]



Y =		
	H	DMTF
	CH_3	DMTA
	CH_2CH_3	DMTP
	$CH(CH_3)_2$	TMTP
	F	DMTCF
	Cl	DMTCCl
	CF_3	DMTCF$_3$

Figure 1. 10 Thioamides studied on reference [38].

The authors of this work calculated through temperature-dependent gas-phase ^{1}H NMR spectra the free activation energies, $\Delta G^{\ddagger}_{298}$, of the C-N rotation in the thioamides. Experimentally, a higher $\Delta G^{\ddagger}_{298}$ value for DMTA (18.0 kcal/mol) than for DMTCF$_3$ (17.2 kcal/mol) was found, and this fact is explained on the basis of a higher steric effect of the CF_3 group when compared to CH_3. To further explore the changes in atomic charge and polarity of the thiocarbonyl bond when electron-withdrawing substituents are present, the authors performed *ab initio* calculations at the 6-31+G* level on thioformamide, thiocarbamyl fluoride, and thiocarbamyl chloride (and the related amides). They found small changes on the polarity of the C=S bond, maintaining a positive charge on the thiocarbonyl carbon atom, and they explain that the *ab initio* results are consistent with a small effect of electron-withdrawing substituents on thioamides, being the rotational barrier in *N*,*N*-dimethylthioamides extremely sensitive to the steric features of the thiocarbonyl substituent.

Vassilev and Dimitrov have performed a similar study on thioamides X-C(S)N$(CH_3)_2$ (X = H, F, Cl, CH_3 and CF_3) checking the influence of the X substituent in the C-N bond rotational barriers at the MP2(fc)/6-31+G*//6-31G* and MP2(fc)/6-311++G**//6-311++G** levels of theory and compared with literature NMR gas-phase data.[39] The most significant structural changes found in the process of rotation are that the nitrogen is pyramidalized, the C-N bond lengthens by 0.07-0.10 Å and the C=S bond shortens by 0.05 Å. Similar calculations performed on related amides showed a shortening of the C=O bond length of about 0.01-0.02 Å, indicating that the thiocarbonyl group is relatively more affected by the rotation in comparison to carbonyl group in the oxoamides.

The experimental rotational barriers of the studied compounds in the gas phase follow the trend: H > F > CH_3 > CF_3 > Cl and correlate mainly with the substituent size and not with the substituent electronegativity. The calculations carried out indicate that the repulsion between X and the *anti* CH_3 group (*anti* refers to the relative position with

respect to the sulfur atom) is mainly responsible for the differences in the rotational barriers in thioamides.

3.2 Solvent effects.

The nature of the solvent is an additional influence to the rotational barrier since the charge-separated structure of the rotational ground state is stabilized by polar solvents. It is expected that the barrier heights will be increased with more polar solvents.

Wiberg and Rush have studied solvent effects on the C-N rotational barriers of *N*,*N*-dimethylthioformamide (DMFT) and *N*,*N*-dimethylthioacetamide (DMTA) both theoretically (*ab initio*) and experimentally (NMR).[36]. The authors find a good correlation between the experimental and theoretical data obtained at the level G2(MP2) in gas-phase. The solvent effects are satisfactorily modeled *via* the SCI-PCM reaction field model[40] at the HF/6-31+G* level of theory for many aprotic, nonaromatic solvents that do not engage in specific interactions with the solute molecules. The C-N bond rotation may occur via both TS1 and TS2, and the final calculated barrier heights include the contribution from the two paths. The experimental values for DMTA are uniform, about 0.4 kcal/mol higher than those of the calculated barriers. In the case of DMTF the experimentally observed values are close to the calculated barriers. In both cases, the agreement between the calculated and observed rotational barriers is satisfactory. The conclusion that the authors reach is that the solvent effects on the rotational barriers are considerably larger for DMTA than for DMA, and this results from the larger ground-state dipole moments for the thioamides than for amides. This fact correlates well with a larger dipole moment of the thioamide and its larger change in dipole moment on going to the transition state as compared with DMA.[15,17] The dipole moments for the transition state are similar for the two systems.

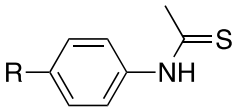
Kaur et al. have studied solvent effects using self-consistent reaction field calculations at B3LYP/6-31+G* level on the value of the C-N bond rotation of C-substitued amides, thioamides and selenoamides.[11] They found that the differences in dipole moments of ground states and transitions states both in gas phase and solvation increases from amide to thioamide and from thioamide to selenoamide. The dipole moment of substituted amides and their thio- and seleno-analogs undergo variations, which are the result of variations in electronegativity, polarizability and relative orientations of different atoms in a given conformation. The smaller difference in dipole moments of ground states and transition states of amides leads one to expect smaller solvent effect on the rotational barriers. The effect of solvents is more prominent in selenoformamide, thioformamide and formamide than in respective substituted amides. The rotational barriers increase with increase in polarity of solvent, thereby suggesting the role of electrostatic interactions in solution phase.

Combined *ab initio* quantum mechanical, molecular mechanical (QM/MM) and molecular mechanical Monte Carlo simulations, followed by BLW-based two-state model analyses, has been performed to study the behavior of thioformamide and formamide in aqueous solution.[32] In this work it is found that on average, about three or five water molecules are found to form hydrogen bonds with the carbonyl oxygen or sulfur in the first hydration shell, while two water molecules are found to solvate the amino group in solutes. In the analysis of the solvent-solute interaction energies it is found that the thioformamide interacts more strongly with water molecules than

formamide. There are interesting structural changes of solutes from gas phase to solution such as the shortening of the C-N bond in both cases and lengthening of the C=E (E = O, S) bonds. This strongly implies the enhancement of resonance and the increasing role of the structure **1b** of Figure 1. 1 in good agreement with the chemical intuition that the ionic structure will be favored in polar solutions.

3.3 Influence of remote substituents.

Galabov et al[41] have used density functional theory 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 (Figure 1. 11). Now, for the planar geometry it is possible to distinguish two isomers because the amide nitrogen atom has two different substituents (the examples commented above have two hydrogen atoms or two methyl substituents).



R = H, CH_3, OCH_3, OC_2H_5, Cl COOH, OH, NH_2, NO_2

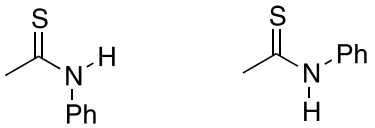


Figure 1. 11 *N*-substituted thioacetanilides

Among the structural parameters of the optimized structures, the authors focus on the amide C-N bond length, $r_{C\text{-}N}$, because this parameter can be considered as a quantity characterizing the strength of the bond and could, therefore, be related to the barrier of rotation. On a previous work, the same group have studied the rotation of *para*-substitued acetanilides[42] and by comparison of the bond length $r_{C\text{-}N}$ in both families of compounds, a shorter distance is found in thioacetamides, which suggests a stronger bond that would involve higher barriers of rotation. 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 (deviations from planarity are < 3º). The *cis* form is nonplanar, and the authors find values for the dihedral angle between the -CS-NH- group and the aromatic ring in the range of 33°-57°. Similar structural features are also found in the substituted acetanilides. The calculations performed for Galabov et al. show a very small difference between the energies of the *cis* and *trans* forms in the range of 0.03-0.63 kcal/mol, indicating that both rotameric forms should be populated at room temperature as it is found experimentally.[43–46] In the theoretical calculations 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. Nevertheless, the authors consider only the smallest barrier because the conformational change is more likely to occur via the lower-energy transition state. The comparison of the rotational barriers calculated for thioacetanilides with the respective acetanilides showed higher values for thioacetanilides, and the influence of the remote

substituents in the aromatic ring over the rotational barriers is almost twice as high in the thioanilides (Table 1. 3). The authors explain these differences based on the electronic structure of the compounds at equilibrium and also on its dynamics with the internal rotation around the C-N bond (see below). Steric hindrance effects that result from the size of the S atom in the thioacetanilide series can be ruled out because of the almost perfectly planar structure for the *trans* conformers. For the *cis* conformers, the equilibrium structure is nonplanar, evidently because of the steric interaction between the methyl group and the *ortho* H atom.

Table 1. 3 B3LYP/6-31G(d,p) Calculated rotational barriers in *para*-substituted thioacetanilides and acetanilides[41]

	$\Delta E = E_{TS2} - E_{trans}$[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 the differences between the energy of the TS2 transition state (E_{TS2}) and the energy of the *trans* conformer (E_{trans}).

The analysis of the values of the Table 1. 3 reveals that the presence of electron-donating substituents (OCH_3, NH_2) increases the differences in barrier heights, while the presence of strong electron-withdrawing substituents (COOH, NO_2) diminishes this difference, being practically equal in the case of NO_2. These findings can be explained in terms or resonance interactions in the systems. The electron-donating substituents make more accessible the structure **1b** of Figure 1. 1 resulting in an increased barrier of rotation. Inversely, the electron-withdrawing substituents hamper the electronic delocalization of the lone pair of the nitrogen atom resulting in a lower rotational barrier.

There are correlations between the theoretically evaluated barriers of rotation in the studied thioacetanilides and intrinsic structural and electronic parameters of the thioamide group. For example, there is a good linear relationship between the C-N bond length (related to the strength of the bond) and the energy barriers ΔE. Nevertheless, the range of variation of r_{C-N} is very close in both anilides and thioanilides (0.013 Å) indicating that this length variation does not provide a sufficiently sensitive basis for rationalizing the differences in rotational barriers that are induced by the substituents. The variation of barrier heights can also be linked to the charge rearrangements in the -CX-NH- (X = S, O) moiety. Linear correlations dependences between rotational barriers, ΔE, and the NBO charge shifts at the S and O atoms induced by the aromatic substituent are found (charge shifts are referred to the equilibrium structure of the *trans* conformers, Figure 1. 12).

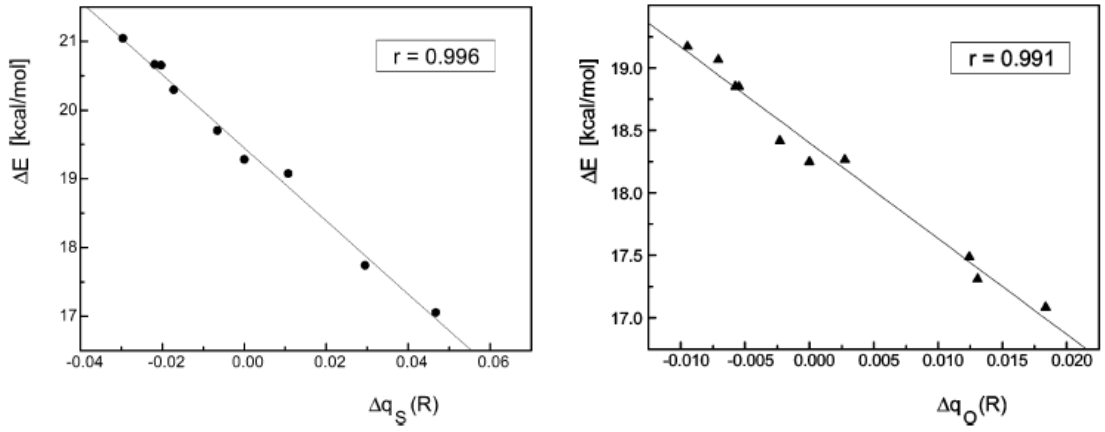


Figure 1. 12 Dependence of rotational barriers (ΔE) on shifts of NBO charges at the S and O atoms (Δq_S and Δq_O) induced by aromatic substituents in thioacetanilides (left) and acetanilides (right)[41]

In these correlations it is found that the same substituents induce much greater charge shifts in the thioacetanilide series than in the respective acetanilides and also it is found that 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. Finally, the analysis of the charge shifts upon rotation from the ground state to the transition state indicates 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 located 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 in which the conjugative effects are strong in the *trans* planar structures while being essentially eliminated in the transition states. The relationships between ΔE and shifts of the NBO charges show that the linear correlation is 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. Similar conclusions are reached by analyzing the atomic charges at equilibrium.

Interestingly, the influence of the substituent depends on the position of the aromatic group bonded to the thioamide. When the aromatic group is bonded to the thioamide nitrogen, electron-donating substituents on the ring increase the barrier of rotation and electron-withdrawing substituents decrease the rotational barrier (as described by Galabov et al.[41], see above). But when the aromatic group is bonded to the thiocarbonyl carbon of the thioamide (Figure 1. 3) the more electron-withdrawing groups on the ring tend to increase the thioamide rotational barriers.[5]

A recent work of Śmiszek-Lindert et al.[47] reports the comparative study of *m*-acetotoluidide and *m*-thioacetotoluidide. The authors study the models at the B3LYP/6-311++G(d,p) and B3LYP/6-311++G(3df,2pd) and they find good correlation between the experimental and the optimized structures, as well as good agreements in vibrational calculations and experimental FT-IR and FT-Raman spectra. Nevertheless, in this work a very small value for the barrier of rotation around the C-N bond of the thioamide is

reported (1.49 kcal/mol) when compared with the value reported by Galabov et al. for the very related compound with the methyl group located in *para* position (19.70 kcal/mol, Table 1. 3). Although the bases used are different, the reported difference in energy is huge to be justified by the change of basis. In addition, the value of the energy of the rotation for the *m*-acetotoluidide (3.9 kcal/mol) is bigger than the value of the related thioamide, which is in contrast with the examples found, and still it is a small value when compared with the one calculated by Galabov (18.42 kcal/mol, Table 1. 3) for the similar *p*-acetotoluidide.

3.4 Photoisomerization.

Helbing et al. have studied both experimentally and theoretically the photoisomerization of the trans form of *N*-methylthioacetamide (Figure 1. 13).[48] *Ab initio* CASPT2//CASSCF photochemical reaction path calculations indicate that, *in vacuo*, the *trans* → *cis* isomerization event takes place on the S_1 and/or T_1 triplet potential energy surfaces and is controlled by very small energy barriers, in agreement with the experimentally observed picosecond time scale.

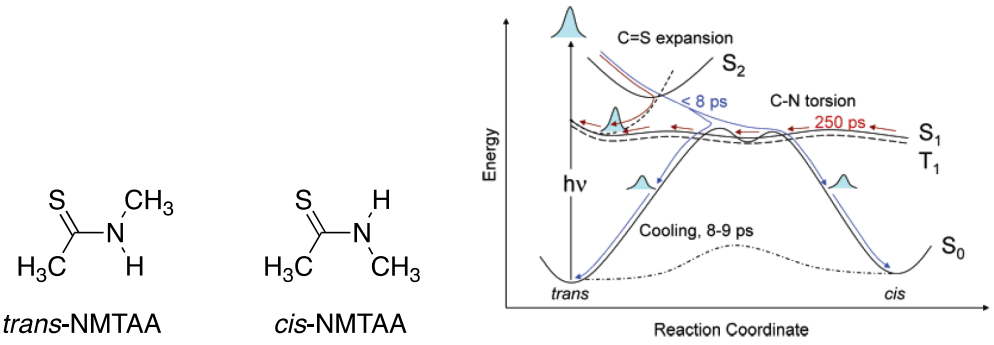


Figure 1. 13 Isomers of the *N*-methylthoacetamide and schematic representation of the photoisomerization reaction of trans-NMTAA[48]

The *trans* stereoisomer is more stable by 1.9 kcal/mol. Two fully asymmetric S_0 transition states describe the *trans* → *cis* thermal isomerization reaction. They are located 24.9 and 20.7 kcal mol^{-1} above *trans*-NMTAA, respectively. *Ab initio* CASPT2//CASSCF reaction path computations for π-π* excitation of *trans*-NMTAA yield consistent mechanistic information on the *trans* → *cis* isomerization of NMTAA. The initial S_2 population evolves on S_2 mainly via a C-S bond expansion (and out-of-plane deformation) leading to efficient $S_2 \rightarrow S_1$ decay in the region of the S_2/S_1 conical intersection. Relaxation on S_1 delivers the system to a very flat region of the potential energy surface, characterized by multiple conformers and multiple S_1/S_0 conical intersections located a few kcal/mol above them. Decay to the ground state may then occur directly via the S_1/S_0 conical intersections or indirectly. Approximately half of the excited molecules seem to follow the direct relaxation pathway and return to the electronic ground state with a time constant of less than 7 ps. The second half of the excited molecules become temporarily trapped in an electronically excited state and reach the electronic ground state with a much longer time constant of ~250 ps. This population trapping can be the result of either competition between vibrational energy relaxation on S_1 and $S_1 \rightarrow S_0$ electronic decay or competition between fast $S_1 \rightarrow S_0$ decay and a somehow slower relaxation process via the triplet states. On both the fast and the slow time scale, *cis*-NMTAA is formed with a quantum efficiency of 30-40%.

Olivucci et al. establish that the final ground-state conformation of NMTAA is predetermined by the molecular geometries of the S_1/S_0 conical intersections and T_1/S_0 intersystem crossings and is therefore independent of the followed route, provided nearly full sampling of the torsional coordinate in S_1 and/or T_1 is possible prior to decay.

3.5 C-N bond rotation in complex systems.

The rotational studies around C-N bonds on thioamides are not studied only on simple systems. Kleinpeter et al.[49] have studied both experimentally and theoretically amino-substituted thio(seleno)acrylamides. The possible isomers of the skeleton studied are depicted in Figure 1. 14.

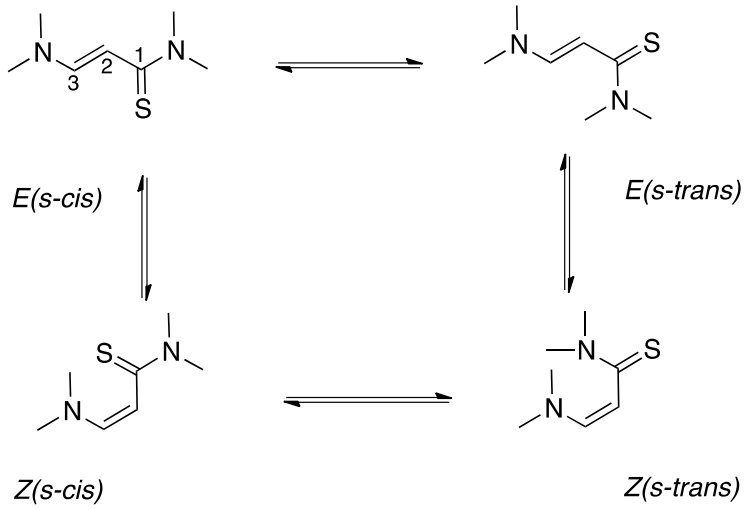


Figure 1. 14 Rotational isomers of thioacrylamides[49]

The compounds exist as preferred *E(s-cis)* isomers, and the additional isomers observed when N(Me)Ph substituents are present were assigned using the GIAO *ab initio*-calculated ring current effect of *N*-phenyl.

Experimental rotational barriers have been calculated using NMR techniques, but the theoretical calculations (at different levels of theory including *ab initio* and DFT) have been used to confirm the experimental observations. As discussed in other works the values of the barriers of rotation found in amino-substituted thioacrylamides are smaller than in seleno analogues due to the higher polarizability of the bigger selenium atom.

By means of the NBO analysis the occupation numbers of the lone electron pairs of N-1/N-3, of the bonding/antibonding π/π^* orbitals of the central $C_1=C_2$ partial double bond and of the antibonding π^* orbitals of the C=S bonds were calculated and shown to quantitatively describe thioamide/vinylogous thioamide resonance. Thus, similar $\Delta G_c^{\ddagger}$ values for C_1-N and C_3-N restricted rotations do not indicate the same amount of the two resonance interactions as thioamide resonance proved to be much stronger. However, the difference to the vinylogous resonance is balanced by additional N-1 lone pair/$\pi^*_{(C1,C2/N2)}$ orbital interactions.

Fuertes et al. described a dynamic behavior in solution of (1,3-Dithiol-2-ylidene)ethanethioamides.[50] These compounds were studied by a combination of dynamic NMR, single crystal X-ray diffraction and DFT modeling of the dynamic behavior observed in solution. The bigger size of the substituents of the thioamide is the reason of the appearance of additional factors to understand the energetics of the C-N bond rotation. The steric hindering of the crowded substitution at the central amine group was found to be the reason for the presence of permanent atropisomers.

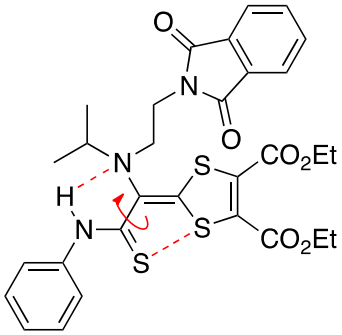


Figure 1. 15 Rotational bond and S-S hypervalent bonding interaction[50]

The absolute minimum found in the optimization of the model used for the theoretical study (Figure 1. 15) displays a planar geometry on the thioamide environment in good agreement with smaller thioamides described above. This absolute minimum displays a distance of 1.999 Å between the hydrogen atom of the thioamide group and the amine nitrogen atom which is in the range of the hydrogen bond interactions, and it can be classified as a moderate−weak hydrogen bond.[51] Although several bond rotations can be proposed to explain the dynamic behavior observed in solution, the rotation that shows a better agreement with the experimental values is the rotation about the C-N bond of the thioformamide. For the compound used as model an experimental value of 14.85 kcal/mol was determined in comparison with 13.92 kcal/mol calculated in gas phase at the theory level B3LYP/6-31G(d). The consideration of the solvation effects with a PCM model at the level of theory B3LYP/6-311G(2d,p)//B3LYP/6-31G(d) afforded a free energy value of 12.20 kcal/mol.

A closer inspection of the electronic structure by using the NBO population approach analysis was performed for the evaluation of the electronic delocalization. These calculations clearly indicated the presence of two lone pair orbitals formally attached at the thiocarboxylic sulfur atom and to the dithiafulvene sulfur atoms. The nature of one of these orbitals on each sulfur atom is a pure *p*-type [$lp_p(S)$], having the orbitals of the sulfur atoms of the dithiafulvene a low electron occupancy of 1.65 and 1.68 e, indicating the electron-donating capacity for this orbital. Delocalizing interactions evaluated by a second-order perturbation approach revealed that the lone pair orbital located at the dithiafulvene sulfur atoms contributed to a resonance interaction with double bond C(1)=C(2) (see Figure 1. 16 for numbering) $lp_p(S) \rightarrow \pi^*_{C-C}$.

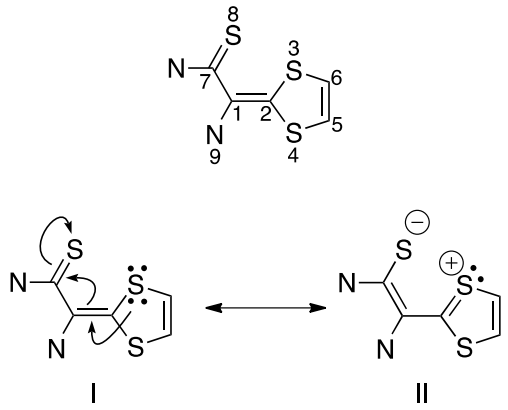


Figure 1. 16 Labeling of the atoms used for the NBO analysis[50]

The computed $E^{(2)}$ interaction value was 26.1 and 23.3 kcal/mol for sulfur atoms S(3) and S(4), respectively. Interestingly, in the analysis of more delocalizing interactions, it was possible to find a second delocalization of the pair of electrons located at the bonding orbital π_{C-C} involving atoms C(1) and C(2) with the double bond C(7)=S(8), $\pi_{C-C} \rightarrow \pi^*_{C-S}$. In this second delocalization the computed $E^{(2)}$ interaction value was 19.0 kcal/mol. The combination of these two delocalization events was in good agreement with the resonance structures I and II shown in Figure 1. 16, and both structures accounted for the planar geometry found in this structure. In addition, the atomic charges obtained by using the natural population analysis (NPA) approach revealed a positive charge +0.34 located at the sulfur atom S(3) and a negative charge −0.15 located at the tioamide sulfur atom S(8), in good agreement with the resonance structure II of Figure 1. 16. These opposite charges reinforced the hypervalent interaction through electrostatic attraction.

A conformational study was performed for proline (Pro) derivatives shown in Figure 1. 17 to examine the effects of oxygen-to-sulfur and oxygen-to-selenium isosteric substitutions on conformational preferences and prolyl cis-trans isomerizations of Pro-containing peptides in water.[52] In this review we are only going to comment the results of the effects of oxygen-to-sulfur substitutions.

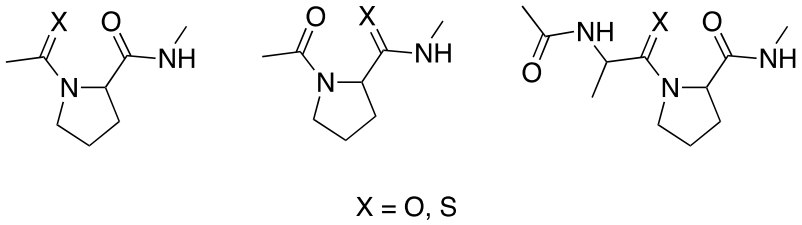


Figure 1. 17. Chemical structures of modeled compounds in reference [52]

The isosteric replacement of a peptide bond by a thiopeptide bond at the preceding residue of the Pro residue in the first model in Figure 1. 17 (i.e., the *N*-terminus), resulted in changes in the preferences of the backbone conformation and puckering of the proline residue in Ac-Pro-NHMe (X = O). In particular, the up-puckered polyproline II (P_{II}) structure was energetically, enthalpically, and entropically preferred for Ac-Pro-NHMe, whereas the down-puckered P_{II} structure was energetically and enthalpically preferred for S substituted Pro-dipeptides. In the second model of the Figure 1. 17, the substitution of oxygen by sulfur at the C-terminus of the Pro residue, the thiopeptide

resulted in puckering of the proline residue in Ac-Pro-NHMe. In the third model of Figure 1. 17, Ac-Ala-Pro-NHMe, open conformers with the *trans* prolyl peptide bond were preferred, and the substitution of oxygen by sulfur leads to an up-puckered 3_{10}-helical structure for the Pro residue.

The rotational barriers to the prolyl *cis–trans* isomerization of Ac-Pro-NHMe and Ac-Ala-Pro-NHMe increased with isosteric replacements at the *N*-terminus in the order O < S. However, the isosteric replacement at the *C*-terminus did not alter the rotational barriers to the prolyl *cis-trans* isomerization of Ac-Pro-NHMe.

4. ROTATIONAL BARRIERS OF N-SUBSTITUENTS

Rotation around other bonds different to the C-N amide bond have been modeled. Wiberg and Rush have studied the methyl rotational barriers in amides and thioamides focusing on the C-N bonds of *N*-methyl and *N*,*N*-dimethyl.[53] As shown in Figure 1. 18 several conformers can be proposed for *N*-methylthioformamide, and *N*,*N*-dimethylthioformamide, (analogous forms can be proposed for *N*-methylthioacetamide and *N*,*N*-dimethylthioacetamide, but considering the rotation of the acetyl methyl group as well). According to the relative orientation of the *N*-methyl group and the sulfur atom in *N*-methylthioformamide, *E*- and *Z*-forms can be proposed. Additionally, for each of these orientations the relative rotamers of the methyl group has to be taking into account, and a second symbol refers to a methyl hydrogen being either *syn* (*s*) or *anti* (*a*) with respect to the thiocarbonyl group. In the *E*-form of the *N*-methylthioformamide, the methyl rotational barrier is somewhat reduced as compared to *N*-methylformamide (0.47 kcal/mol for *N*-methylthioformamide and 0.88 kcal/mol for *N*-methylformamide). Following the comparison between *N*-methylthioformamide and *N*-methylformamide, it is interesting to highlight the increase in the barrier for the *Z*-form, which is over 1 kcal/mol greater than that for the corresponding formamide (1.49 kcal/mol for *N*-methylthioformamide and 0.33 kcal/mol for *N*-methylformamide). The steric hindrance of the bigger sulfur in comparison to the size of the oxygen can be the reason of a bigger repulsive interaction between the sulfur and an eclipsed hydrogen of the methyl group of the *Z*-form. These higher repulsive interactions in the thioamides are reflected in the C-N-C bond angles. For the *N*-methylformamide the values of these angles are 120.7º in the isomer *Za* and 123.0º in the isomer *Zs*, while for the *N*-methylthioformamide the values of the same angles are 122.4º in the isomer *Za* and 125.0º in the isomer *Zs*. The same factor is the responsible of the differences found on the geometry of the lowest energy conformers of the N,N-dimethylthioformamide and its analogous amide. In the amide, the *Z*-methyl group is rotated so that a methyl hydrogen is eclipsed with the carbonyl oxygen. In the *N*,*N*-dimethylthioformamide the *cis*-Me-C-N-H torsional interaction is greater than the O···H nonbonded interaction, but the *Z*-methyl group is rotated so that it is not eclipsed with the sulfur, which may be related to the larger size of the sulfur, making the S···H non-bonded interaction the dominant term. Similar facts have been described for thioacetamides. The *E*-forms of *N*-methylthioacetamide show similar relative energies as for *N*-methylacetamide indicating that the replacement of oxygen by sulfur has little effect on the barrier. The reason of this little effect is the long distance between the *N*-methyl group and the sulfur. However, there are marked changes in the relative energies of the *Z*-forms. In *Z*-forms the proximity between the O/S atom and the *N*-methyl group is bigger than in *E*-forms and the rotamers of *N*-methylthioacetamide having a methyl hydrogen eclipsed

with the sulfur display an increase in energy of about 1.5 kcal/mol with respect to the alternate forms. The *N*,*N*-dimethylthioacetamide has a ground-state rotamer with a rotated *Z*-methyl avoiding proximity between the sulfur atom and the hydrogen atoms (in the analogous *N*,*N*-dimethylacetamide the same Z-methyl locates a hydrogen atom eclipsed with the oxygen atom).

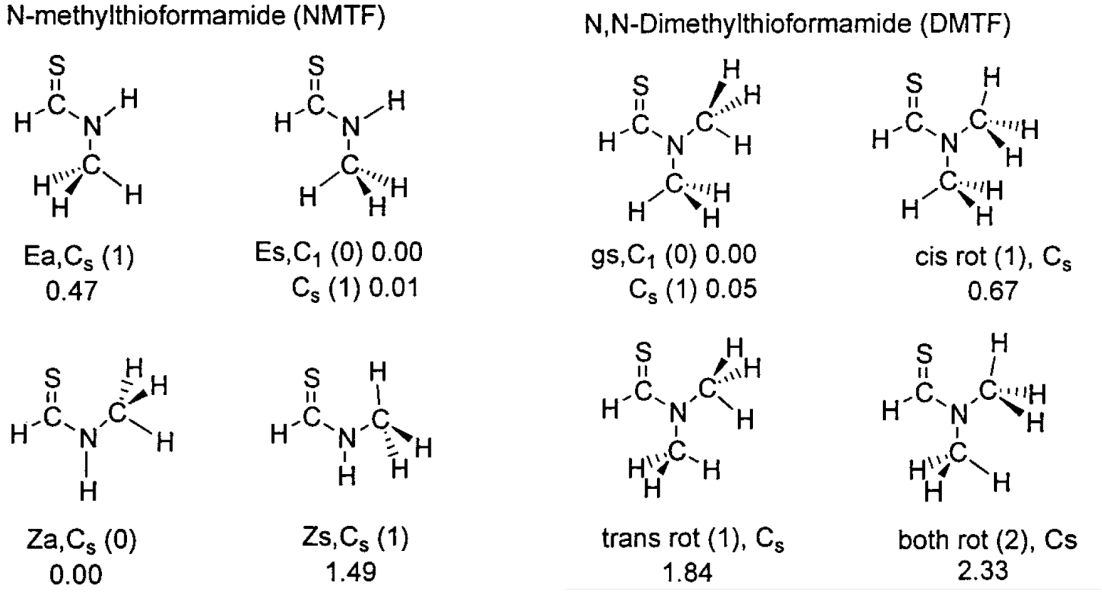


Figure 1. 18 Rotamers of *N*-methylthioformamide and *N*,*N*-dimethylthioformamide [53]

5 CONJUGATION WITH DIFFERENT SUBSTITUENTS

Velkov et al.[54] have studied the interaction of the carbonyl and thiocarbonyl group of the amide and thioamide of *o*-coumaric acid using HF and DFT theoretical methods.

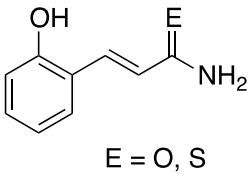


Figure 1. 19 Amide and thioamide of *o*-coumaric acid.

Several structural parameters show that there is conjugation between the *o*-coumaric acid and the amide or thioamide. One of them is the length of the C-N bond, which is found to be longer in the *o*-coumaric derivatives than amide and thioamide. The conjugation degree in the thioamide is considerably higher than that in the amide. For example, the calculated bond length for the double C=C bond connecting the aryl group with the carboxylic (or thiocarboxylic) group is shorter for the thioamide. Data based on NBO analysis point toward the same direction (see Table 1. 4). The lone pair delocalization of the nitrogen atom (estimated through second-order energies on NBO analysis) is more effective in the thioamide than in the amide. The direction of this delocalization is toward the C=O and the C=S double bonds, respectively. The interaction energy between the electron pair of the C=C bond (connecting the aryl group with the amide/thioamide fragment) and unoccupied neighboring orbitals shows a

favored direction of conjugation which is toward the amide/thioamide group.

Table 1. 4 Some second-order energies (in kcal/mol) obtained by the B3LYP and HF methods and basis 6-31+G(d) [54]

Compound	Method	Second-order energies		
		$n_{N10} \rightarrow$ to	$\pi_{C7=C8} \rightarrow$ to	$n_{O12} \rightarrow$ to
Amide	UB3LYP	$\pi^*_{C=O}$ (55.47)	$\pi^*_{C9=O11}$ (19.41) $\pi^*_{C5=C6}$ (10.04)	$\pi^*_{C1=C2}$ (28.38)
	UHF	$\pi^*_{C9=O11}$ (39.00)	$\pi^*_{C9=O11}$ (13.02) $\pi^*_{C5=C6}$ (4.79)	$\pi^*_{C1=C2}$ (22.80)
Thioamide	UB3LYP	$\pi^*_{C9=S11}$ (68.84)	$\pi^*_{C9=S11}$ (23.72) $\pi^*_{C5=C6}$ (10.41)	$\pi^*_{C1=C2}$ (34.81)
	UHF	$\pi^*_{C9=S11}$ (58.81)	$\pi^*_{C9=S11}$ (18.26) $\pi^*_{C5=C6}$ (5.29)	$\pi^*_{C1=C2}$ (23.30)
Amide radical	UB3LYP	$\pi^*_{C=O}$ (28.88)	$\pi^*_{C9=O11}$ (10.91)	n^*_{C1} (69.17) $\pi^*_{C1=C6}$ (10.43) $\pi^*_{C1=C2}$ (9.34)
	UHF	π^*_{C9} (54.56)	n^*_{C9} (28.89)	$\pi^*_{C1=C2}$ (59.83) $\pi^*_{C1=C6}$ (11.41)
Thioamide radical	UB3LYP	$\pi^*_{C9=S11}$ (36.35)	$\pi^*_{C9=S11}$ (14.47)	n^*_{C1} (72.03) $\pi^*_{C1=C6}$ (9.50) $\pi^*_{C1=C2}$ (8.43)
	UHF	$\pi^*_{C8=C9}$ (54.70)	$\pi^*_{C9=N10}$ (2.36) $\pi^*_{C8=C9}$ (2.12)	$\pi^*_{C1=C6}$ (13.95) $\pi^*_{C1=C2}$ (12.86) r^*_{C1} (10.42)

Symbols σ, π, n (lone pair), and r (Rydberg orbitals), and σ^*, π^*, n^* and r^*, are used for notation of the filled and vacant NBOs of the formal Lewis structures.

6. THIOPEPTIDES.

Thioamide substitution into peptide structures has been explored by several groups. Artis and Lipton have studied the Potential Energy Surface of four model dipeptides containing thioamide bond (Figure 1. 20).[55] The study has been developed at the HF/6-31G* level of theory, and then they have used selected regions as starting points for full geometry optimization at the HF/6-31G* and MP2/6-31G* levels. Both levels of theory afford similar results with small changes in relative energies, that were small when compared to the consequences of sulfur substitution.

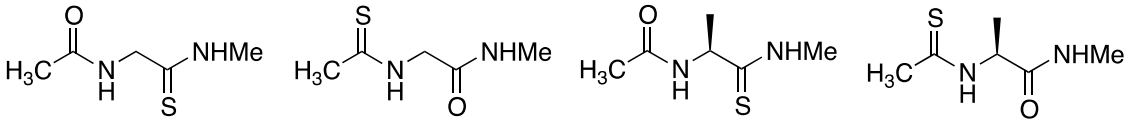


Figure 1. 20 Model dipeptides studied by Artis and Lipton

The authors find that the conformations of the *C*-terminal thioamides were generally close to those of the corresponding peptides, the *N*-terminal thioamides displayed markedly different conformational behavior. The changes in the conformational profile of thioamide-containing peptides appear to result from a combination of the decreased hydrogen bonding-accepting ability and increased size of sulfur versus oxygen and lengthening of the C=S bond in the thioamide as compared to the C=O bond in an amide. The predominant effect of the substitution of sulfur is on the residue following

the thioamide bond in the sequence (i.e., to the *C*-terminal side), and serves to strongly bias this residue toward a conformation in the region of negative ϕ and positive ψ.

Tran et al.[56] have studied the conformational analysis of thiopeptides. The authors of this work found that the hydrogen bond lengths calculated at the HF/6-31G* level of theory are much longer than the corresponding hydrogen bond lengths for normal peptides when the bulkier sulfur atom acts as hydrogen bond acceptor in the C_5 conformation or in the C_7^{ax} and C_7^{eq} conformations in a vacuum environment. For this reason, the ϕ, ψ dihedral angles of the C_5, C_7^{ax} and C_7^{eq} conformations of thiopeptides change to accommodate the longer hydrogen bonds. The authors also predict that upon thio substitution at the amino terminal, the C_7 conformations will be disfavored relative to the C_5 conformations. However, upon thio substitution at the carboxyl terminal, the C_7 conformations are favored relative to the C_5 conformation. The authors hypothesize that the change of the type of hydrogen bonding can be the reason for this switch in conformational preference. The (ϕ, ψ) conformational energy maps for the glycine, alanine, and thio-substituted dipeptides calculated using several relative permitivities to simulate the conformations in solution indicated that thio substitution does restrict the conformations available to amino acids residues in peptides. The areas on the (ϕ, ψ) energy maps for the thiopeptides, which will be accessed spontaneously under standard temperature and pressure conditions, are considerably smaller than the corresponding areas for normal peptides. Thio substitution at the amino terminal and at the carboxyl terminal introduces an unfavorable interaction that restricts some conformations. This restriction of conformations does not mean that the thiopeptides show only one conformation, and some of them can prefer one or two conformations, as it has been demonstrated by Tran et al. at the CFF91 force field level of theory.[57,58]

Molecular dynamics simulations have been performed by Tran et al.[59] to study the effects of thio substitutions on the conformation on dipeptides finding that thio-substitution favors conformations were $\phi < 0$ because of the deeper β and right-handed α-helix. The same group have developed molecular dynamics simulations to study the effects of thio substitutions on the conformation on of α-helices, 3_{10}-helix, and their relative stability on longer polipeptides.[60] The dynamic simulations show that the most prominent structural change to the α-helices and 3_{10}-helices conformations introduced by the thio substitution is the increased hydrogen bond distance from 2.1 to 2.7 Å. Consequently, there is a modification in the value of the ϕ and ψ dihedral angles to accommodate for the longer C=S···H-N hydrogen bond. The conformation 3_{10}-helix is more likely in thiopeptides than in normal peptides. The 3_{10}-helix conformation is favored because the hydrogen bond conformation can adopt more conformations (it is more flexible) relative to the α-helix and there is an increase of entropy. This differential flexibility is more apparent upon thio substitution.

Lee et al.[61] have examined the effect of thioamide substitution into azapeptide For-AzaGly-NH_2 (Figure 1. 21).

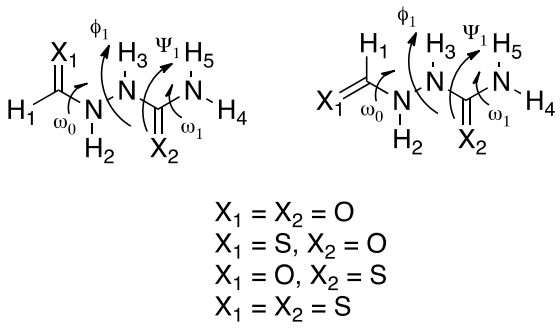


Figure 1. 21. Chemical structures of For-AzaGly-NH_2, For-[ΨCSNH]-AzaGly-NH_2, For-AzaGly-[ΨCSNH]-NH_2, and For-[ΨCSNH]-AzaGly-[ΨCSNH]-NH_2 [61]

Through the analysis of the Potential Energy Surface, the authors find the minimum energy conformations that were optimized. The minima prefer the secondary structures in proteins such as the β-strand, polyproline II, βI(II), or βVI-turn scaffolds. The analysis of the bond order for the N-N (ϕ_1) and N-C (ψ_1) bonds demonstrates that these bonds have close to single bond character. The barriers of the N-C (ψ_1) bond are < 10 kcal/mol, suggesting that the ψ_1 bond is partially restricted at the 0 ± 30° or 180 ± 30°. The rotational barriers of the N-N (ϕ_1) bond are estimated in the range from about 4 to 24 kcal/mol, depending on the orientation of the formyl group and the ψ_1 angle of 0 or 180° at the B3LYP/6-31G*//HF/6-31G* level. Noteworthy, the rotation about the N-N (ϕ_1) bond as the ω_0 and ψ_1 angles are ≈180°, for the studied structures, shows a single barrier, whose value is about 24 kcal/mol at the B3LYP/6-31G*//HF/6-31G* level. This implies that conformers of minimum energy, corresponding to the β-strand structure, are restricted in these regions.

A theoretical study of the electronic structure of thio-substituted dipeptides and tripeptides has been performed by Joy et al.[62] at the DFT and TD-DFT levels of theory. The substitution of oxygen by sulfur has influence in geometrical parameters including bond lengths and bond angles, and this influence is higher when the substitution occurs at N-terminus. For example, the *N*-terminal substitutions increase the C-S bond distances. Two types of transitions are found in these peptides, n–π^* and π–π^*. In general, the former transition is from the lone pair on sulfur atom to the empty carbonyl group π^* at the other end. The latter is from π electron cloud at the *N*-terminal to the π^* orbital at the *C*-end. The presence of *N*-terminal substitutions is found to give orbitals localized at *N*-terminal, whereas substitutions at other positions are found to have delocalized orbitals shifting the wavelength to a lower region (blue shift).

DFT Theoretical studies performed by Raines et al. on peptides and thiopeptides show an attractive $n \rightarrow \pi^*$ interaction between adjacent backbone carbonyl groups (Figure 1. 22). This interaction stems from the delocalization of the electron pair (n) of a donor group (O, S) into the antibonding orbital (π^*) of a neighbor (thio)carbonyl group. The substitution of an amide donor with a thioamide could increase ligand affinity as a result of enhanced $n \rightarrow \pi^*$ electronic delocalization due to increased overlap and reduced energy difference between the donor and acceptor orbitals.[63–67]

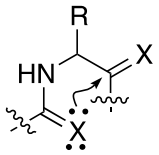


Figure 1. 22 Interaction displaying the n → π* electronic delocalization

7. N-H BOND DISSOCIATION ENTHALPY (BDE).

Kaur et al. have used theoretical methods to study the dissociation enthalpies of amines and amides.[68] Here, we are going to focus on the results in thioamides and the comparison with amides. The N-H BDE decreases in compounds $H_2NC(=X)Y$ in the order of X as O > S > Se for Y = H, F, Cl, CH_3, NH_2, NO_2, CN, OH. For the simplest models (Y = H), the lower N-H BDE in case of $HC(=S)NH_2$ and $HC(=Se)NH_2$ is the result of shift of radical center to S or Se, respectively, along with C=N π-bond formation, as it is suggested by the occupancies of α and β molecular orbitals in the Restricted Open calculations. The substituents can alter stability of molecule and the stability of radical, thereby resulting in the variation in N-H BDE of the molecule relative to that of the reference molecule. Considering substituents at the (thio)carbonyl carbon, in thioamides both electron-donating and withdrawing substituents decrease the N-H BDE relative to $HC(=S)NH_2$, while in amides σ withdrawing substituents like F and π acceptor groups like NO_2 and CN at the carbonyl carbon increase the N-H BDE while the electron donor groups like CH_3, NH_2, Cl and OH decrease the N-H BDE relative to $HC(=O)NH_2$ (Table 1. 5).

Table 1. 5 N-H bond dissociation enthalpies (in kcal/mol) for β-substituted amides $H_2NC(=X)Y$ at ROB3LYP/6-31+G*//B3LYP/6-31+G(d,p) [L1], ROB3LYP/6-311++G(d,p)//B3LYP/6-31+G* [L2], and MP2/6-311++G(d,p)// MP2/6-31+G* [L4] theoretical level [68]

Substituent	L1			L2			L4		
Y	X = O	X = S	X = Se	X = O	X = S	X = Se	X = O	X = S	X = Se
H	111.85	99.30	91.48	114.50	101.56	91.67	113.82	92.67	85.50
F	109.28	95.50	88.22	114.94	97.45	88.04	113.10	92.71	91.33
Cl	110.57	93.42	86.90	112.87	95.32	86.06	111.71	90.70	81.07
CH_3	108.76	95.97	90.06	111.50	98.37	86.99	110.54	90.01	82.05
NH_2	104.49	93.41	88.82	107.21	95.76	89.55	107.35	92.92	85.04
NO_2	116.35	94.42	86.75	118.75	96.76	87.40	114.09	—	—
CN	113.34	—	90.80	116.35	98.63	90.73	114.51	111.96	110.81
OH	109.46	107.20	106.94	113.42	113.36	111.79	112.08	111.22	110.58

For Y = H; X = O N—H BDE is 111.95, 115.88 at G3MP2 and CBS-QB3 level, respectively.
Y = H; X = S N—H BDE is 98.49, 99.60 at G3MP2 and CBS-QB3 level, respectively.
Y = H; X = Se N—H BDE is 91.55 at G3MP2 level.

The effect of different substituents at the nitrogen atom in amides HC(=X)NHY [X = O, S, Se; Y = H, F, Cl, CH_3, NH_2, NO_2, CN, OH] has been analyzed as well. The geometry optimization leads to two minima (*syn* and *anti* conformers) on the potential energy surface, the *syn* being more stable in most cases (some exceptions are *N*-amino and *N*-methyl thioformamides). Considering the most stable conformation out of the two, the N-H BDEs are observed to be lower than the values for $H_2NC(=X)Y$ molecules but the

same trend is conserved with a more pronounced effect than when the substituent is bonded to the carbonyl carbon (Table 1. 6).

Table 1. 6. N-H bond dissociation enthalpies (in kcal/mol) for *N*-substituted amides YHNC(=X)H at ROB3LYP/6-31+G*//B3LYP/6-31+G(d,p) [L1], ROB3LYP/6-311++G(d,p)//B3LYP/6-31+G* [L2], and MP2/6-311++G(d,p)// MP2/6-31+G* [L4] theoretical level [68]

Substituent	L1			L2			L4		
Y	X = O	X = S	X = Se	X = O	X = S	X = Se	X = O	X = S	X = Se
H	111.85	99.30	91.48	114.50	101.56	91.67	113.82	92.67	85.50
F	118.73	79.49	77.05	121.46	82.68	76.14	97.11	80.51	70.82
Cl	94.93	90.49	79.58	98.04	93.21	86.13	100.72	83.45	75.96
CH_3	105.14	96.44	90.27	108.10	99.15	92.69	119.84	102.55	83.58
NH_2	80.74	74.34	71.77	81.35	76.72	73.78	83.03	86.23	80.07
NO_2	107.31	84.17	77.97	109.76	87.01	79.74	110.59	83.27	75.40
CN	113.69	87.66	81.50	116.36	90.08	83.44	112.27	86.71	81.09
OH	82.82	79.49	90.12	86.33	82.98	92.69	88.41	84.44	82.65

8. OTHERS.

Thioamides involved in different chemical processes have been studied using quantum chemical calculations.

4-Thioamidopyridine (4-thiocarbamoylpyridine) is the parent compound of ethionamide (2-ethyl-4-thiamidopyridine, 2-ethylthioisonicotinamide). It is a drug for the treatment of multidrug-resistant tuberculosis. Wysokiński et al. have performed a theoretical study of this compound[69] by full geometry optimization at the B3LYP/6-311G(d,p) level of theory for an isolated molecule and a pair of molecules linked by hydrogen bond (Figure 1. 23). The authors find a good agreement between the experimental structure and the optimized geometry.

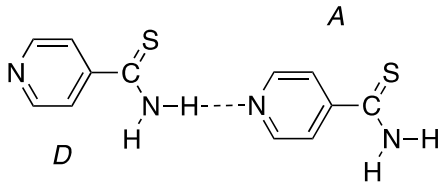


Figure 1. 23 Hydrogen bonded pair of A-D molecules of 4-thiocarbamoylpyridine. *A* denotes proton acceptor and *D* is a proton donor subunit

The formation of the intermolecular hydrogen bond N-H···N_{py} induces changes in the bond lengths of the NH_2-C=S group with a shortening of the C-N bond and an elongation of the C=S bond. The vibrational analysis has been very helpful to assign all the signal of the vibrational spectroscopies that otherwise would be very difficult to do. For example, the vibrational analysis shows that the ν(C=S) stretching vibration contributes mainly to the medium-strong bands at 926 and 725 cm^{-1} in infrared, and 947 and 728 cm^{-1} in the FT-Raman spectrum.

Palmer and Sherwood have performed theoretical studies HF with and without Moller-Plesset correlation effects to discuss the Nuclear Quadrupole Coupling Constants from

microwave spectroscopy and quadrupole resonance.[70] The authors describe that the larger dipole moments from thioamides than the corresponding amides is a function of enhanced resonance in the former. The principal mechanism seems to be the push/pull σ/π effects of the N atom with respect to the CO and CS groups, with S being a better σ-donor than O; however, the effect is still present with formamidine where electronegativity effects are important, so the overall effect is the 2,1,1-π electron contribution to the allylic system from N, C, O(S). The Natural Orbitals localize readily to Localized Orbitals, and these account for the gross magnitudes of the electronic terms in the Electric Field Gradient. However, in the summation with the nuclear terms, the more distant centers still have some defining impact. Hence the general trends for ^{14}N Nuclear Quadrupole Coupling Constants to be higher in amides than thioamides, do emerge from the Localized Orbital analysis.

Velkov et al. have used quantum chemical calculations to study the radical scavenging activity of *o*-coumaric acid thioamide in comparison with the related amide (Figure 1. 24).[71]

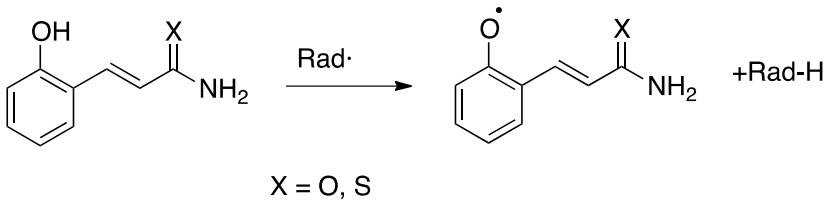


Figure 1. 24 Radical scavenging reaction and structures of *o*-coumaric acid amide and thioamide (and corresponding radicals) [71]

Although the reactivity focus on the relative transformation of a substituted phenol to a substituted phenoxyl radical, the different behavior of the sulfur and the oxygen makes a difference. The HOMO energies also indicate that the thioamide should be a better scavenger than the amide, since ionization should be easier for the thioamide than for the amide. The spin density distribution in the amide and thioamide radicals is in agreement with the conclusions for higher stability of the latter, for example, the spin density at the phenoxyl oxygen in the thioamide radical is smaller by 0.03 than the one at the corresponding atom in the amide radical.

Finally, thioamides have been used as fluorescent probes by Petersson et al. through a mechanism of quenching that can be either Förster Resonance Energy Transfer (FRET) or Photoinduced Electron Transfer (PET).[72–74] Nevertheless, to be best of our knowledge there is only one report by using theoretical modeling to study the behavior of thioamides as probes. In that work, the thioamide (thiourea) sensor has been theoretically modeled[75] using DFT calculations to describe the structure of the complex formed between the probe and Zn^{2+}. The scarce use of theoretical models to understand the behavior of the thioamides as sensors is an attractive field to be developed.

9. CONCLUSIONS.

The structural features of thioamides can be rationalized on the basis of quantum chemical calculations. The planar conformation found is in good agreement with the experimental determinations. Derivations from planarity can be explained as well under

a theoretical point of view by finding the explanation on the nature of the different substituents. The rotation about the C-N bond has been studied under different theoretical approaches and basically all of them agree that the higher charge transfer from the nitrogen to the chalcogen atom, when this atom is heavier, is the reason of the higher contribution of the structure **1b** (Figure 1. 1). Although this fact is counterintuitive in terms of electronegativity concepts, the increasing polarizability of the elements going down on the chalcogen group is the reason of this higher charge transfer when heavier elements are involved.

The calculated C-N rotational barriers in these systems account for two factors: (1) the energy rise due to breaking the partial pπ-pπ bond between carbon and nitrogen and (2) the energy gain due to the $n_N \rightarrow \sigma^*_{C-X}$ negative hyperconjugation in the rotational transition state. The increase in the delocalization $n_N \rightarrow \pi^*_{C-X}$ as going down the period in the group 16 is mainly attributable to the decrease in the energy difference between the energies of the N lone pair and the π^* orbital of C-X bond and that stabilizes the planar conformation. On the other hand, the electronegativity of X strongly influences the $n_N \rightarrow \sigma^*_{C-X}$ negative hyperconjugative interaction and stabilizes the transition state. These two interactions complement each other in increasing the C-N rotational barrier in thioformamide relative to formamide. The effect of the substituents bonded to the carbon atom of the thiocarbonyl atom is mainly steric effects.

The solvent effects calculated reveal that the rotational barrier increases with increase in polarity of the solvent, and this fact suggests electrostatic interactions in solution that are in good agreement with an important participation of the structure of resonance **1b** of Figure 1. 1. Remote substituents have their influence on the C-N bond rotational barrier and, interestingly, this influence depends on the position of bonding of the substituent. When the aromatic group is bonded to the thioamide nitrogen, electron-donating substituents increase the barrier of rotation and electron-withdrawing substituents decrease that barrier. But when the aromatic group is bonded to the thiocarbonyl carbon of the thioamide, the more electron-withdrawing groups tend to increase the thioamide rotational barriers.

Other features of the thioamides have been studied under a theoretical approach. The higher size of the sulfur atom with respect to the oxygen is important in the rotation of *N*-bonded methyl groups in (thio)formamides and (thio)acetamides. In thioamides, both electron-donating and withdrawing substituents at the thiocarbonyl carbon decrease the N-H BDE relative to $HC(=S)NH_2$, while in amides, σ withdrawing and π acceptor substituents at the carbonyl carbon increase the N-H BDE and electron donor groups decrease the N-H BDE relative to $HC(=O)NH_2$. Finally, theoretical calculations have been used to help to understand the behavior of some thioamide compounds in establishing hydrogen bonding, scavenging of radicals or to discuss the Nuclear Quadrupole Coupling Constants.

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