Conformational Preferences and Internal Rotation in Alkyl- and Phenyl-Substituted Thiourea Derivatives

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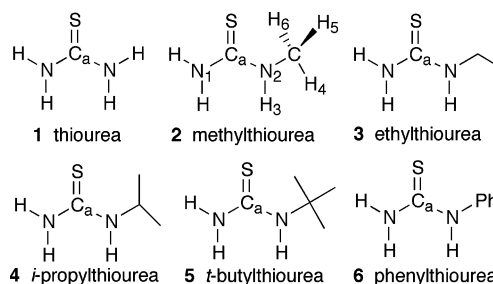
Potential energy surfaces (PES) for rotation about the N−C(sp³) or N−C(aryl) bond and energies of stationary points on PES for rotation about the C(sp²)−N bond are reported for methylthiourea, ethylthiourea, isopropylthiourea, *tert*-butylthiourea, and phenylurea, using the MP2/aug-cc-pVDZ method. Analysis of alkylthioureas shows that conformations, with alkyl groups cis to the sulfur atom, are more stable (by 0.4−1.5 kcal/mol) than the trans forms. All minima adopt anti configurations with respect to nitrogen pyramidalization, whereas syn configurations are not stationary points on the MP2 potential surface. In contrast, analysis of phenylthiourea reveals that a trans isomer in a syn geometry is the global minimum, whereas a cis isomer in an anti geometry is a local minimum with a relative energy of 2.7 kcal/mol. Rotation about the C(sp²)−N bond in alkyl and phenyl thioureas is slightly more hindered (9.1−10.2 kcal/mol) than the analogous motion in the unsubstituted molecule (8.6 kcal/mol). The maximum barriers to rotation for the methyl, ethyl, isopropyl, *tert*-butyl, and phenyl substituents are predicted to be 1.2, 8.9, 8.6, 5.3, and 0.9 kcal/mol, respectively. Corresponding PESs are consistent with the experimental dihedral angle distribution observed in crystal structures. The results of the electronic structure calculations are used to benchmark the performance of the MMFF94 force field. Systematic discrepancies between MMFF94 and MP2 results were improved by modification of selected torsion parameters and one of the van der Waals parameters for sulfur.

Introduction

Thiourea and its derivatives have been the focus of attention in recent years in view of their interesting physicochemical properties and broad range of applications in several chemical disciplines. Certain thiourea molecules have antiviral activity and might be characterized as prospective inhibitors of many enzymes, particularly, HIV-1 reverse transcriptase.[1] As antibacterial and antifungal agents, they have been used in agriculture.[2] In technical applications dithioamide compounds are known to be prospective nonlinear optical materials,[3] corrosion inhibitors for copper and iron in acidic media,[4] and functionalization agents for production of chemically modified resins.[5] Thiourea derivatives have been also reported as potential receptors and ionophores for heavy metal cations,[6] building blocks in the synthesis of heterocyclic compounds.[7] Finally, the strong hydrogen-bonding donor capability of the -N(H)−C(=S)−N(H)- group has been widely exploited in supramolecular chemistry, where it has been used as a building block for anion receptors.[8]

The ability to model the shapes and energetics of thiourea molecules is essential for understanding the chemistry of compounds containing this important functional group. Although some force field models, such as MMFF94,[9] have been parametrized for this moiety, such models have not been tested for their ability to reproduce the geometries and relative energies of substituted thiourea derivatives. In prior conformational analyses of structurally related urea molecules, we found that the default MMFF94 model failed to reproduce the C_a−N rotational barriers and relative energies of cis and trans forms obtained at the MP2/aug-cc-pVDZ level of theory.[10] Marked improvement in the performance of the MMFF94 model was achieved after simple modification to selected torsional parameters. Motivation for the current study came from a desire to evaluate the transferability of these parameters to thiourea systems and to elucidate the similarities and differences between urea and thiourea conformations.

SCHEME 1

1 thiourea   2 methylthiourea   3 ethylthiourea

4 *i*-propylthiourea   5 *t*-butylthiourea   6 phenylthiourea

Herein we report conformational analyses for thiourea (Scheme 1), **1**, methylurea, **2**, ethylurea, **3**, isopropylurea, **4**, *tert*-butylurea, **5**, and phenylthiourea, **6**, performed with second-order Möller−Plesset perturbation theory (MP2). All possible minima generated by rotation about both C_a−N and N−C(alkyl) or N−C(aryl) bonds are considered. Where possible, the results are compared with those obtained from previous electronic structure calculations and with experimental data for geometries and rotational barriers. The results also serve to benchmark and improve the performance of the MMFF94 model. Finally, conformational preferences and rotational barriers in thiourea groups are compared with those found for urea groups.

Theoretical Details

Electronic Structure Calculations. Conformational analysis of the alkyl- and phenylthioureas was performed with the NWChem program[11] using second-order Möller−Plesset perturbation theory.[12] Calculations were done using the correlation-consistent aug-cc-pVDZ basis set,[13] including all electrons in the correlation treatment. Initial geometries were generated by the substitution of sulfur for oxygen and adjusting the length of the C=S bond in optimized structures obtained previously for urea derivatives. The potential energy surfaces, PESs, were

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TABLE 1: Modified MMFF94 Torsional Parameters[a]

dihedral angle	atom types				V_1	V_2	V_3	ref
N−C$_a$−N−H	10	3	10	28	1.800	3.100	0.620	10
N−C$_a$−N−C(alkyl)	10	3	10	1	−0.100	3.100	0.000	10
N−C$_a$−N−C(aryl)	10	3	10	37	1.000	3.800	0.000	10
C$_a$−N−C(aryl)−C(aryl)	3	10	37	37	0.000	3.000	0.000	10
H−N−C(aryl)−C(aryl)	28	10	37	37	0.000	1.100	0.000	10
S−C$_a$−N−H	16	3	10	28	−1.100	6.300	−0.340	this work
S−C$_a$−N−C(alkyl)	16	3	10	1	−5.200	8.500	0.600	this work
S−C$_a$−N−C(aryl)	16	3	10	37	−3.750	6.280	0.000	this work

[a] Barrier heights, V_1–V_3, are given in kilocalories per mole.

obtained by constraining the corresponding dihedral angles (N−C$_a$−−N−X for rotation about the C$_a$−N bond and C$_a$−N−C−X for rotation about the N−C bond, where X = H or C) and fully optimizing the remaining internal coordinates. Intervals of 15 and 30° were used for phenyl and alkyl substituents, respectively. Frequencies were computed at the MP2/aug-cc-pVDZ level to characterize each stationary point as a minimum or a transition state.

Cambridge Structural Database. Experimental average X-ray diffraction crystal structure parameters and distribution of dihedral angles were obtained through analysis of the Cambridge Structural Database (CSD). The CSD program ConQuest[14] was used to identify structures in which at least one of the thiourea nitrogen atoms is substituted by both a hydrogen atom and an alkyl or phenyl group in a cis position with respect to the C=S bond. Searches yielded 118 methyl, 187 CH$_2$CH$_2$X (X is an arbitrary group), 12 secondary alkyl, 6 tertiary alkyl, and 74 phenyl groups when applying constraints of an R factor of less than 10%, no errors, no disorder, and no metal ion coordination at the sulfur. A statistical analysis of the geometric parameters in these structures was carried out with the CSD VISTA program.[14]

Force Field Calculations. The calculations were performed using MMFF94 force field[9] implemented in the PCMODEL molecular modeling software.[15] Comparison of the MP2 results with those obtained from the default MMFF94 model revealed several systematic discrepancies. MMFF94 yields an incorrect picture of the relative stability of cis and trans isomers and overestimates the barrier heights for rotation about C$_a$−N bonds for all cases examined, **1**−**6**. In addition, while MMFF94 does a good job at reproducing the N−C(alkyl) rotational PESs, the position of minima for N−C(aryl) rotation in **6** is significantly different and the barrier heights are greatly overestimated.

The majority of these discrepancies are explained by the use of generalized wildcard parameters for torsional interactions, which depend only on the atom type of the central two atoms.[9] In our prior study of urea molecules, the default MMFF94 parameter set was updated to include the modifications pertaining to C$_a$−N and N−C(aryl) rotation.[10] These modifications were retained, and additional parameters specific for rotation about the C$_a$−N bond in thiourea (S−C$_a$−N−X, X = H, C(alkyl), and C(aryl)) were adjusted to obtain the best fit with MP2 barrier heights and cis/trans relative energies for thiourea derivatives. All modified torsional parameters are presented in Table 1.

One additional change was made to the parameter set. To correct for the overestimated steric interaction when a substituent is cis with respect to the sulfur atom, one of the van der Waals parameters for thiocarbonyl sulfur was modified. The buffered 14−7 form used for the van der Waals potential in MMFF94 requires four parameters, three of which (scaling factors, effective numbers of electrons determined from the Slater−Kirkwood formula) depend on the atomic species rather than on the MMFF94 atom types. To obtain the best agreement, the remaining parameter (atomic polarizability) was adjusted from

TABLE 2: Relative Energies (kcal/mol) for Geometries of 1−6 at Various Levels of Theory

conformer	MP2	MMFF94	MMFF94+
1 anti	0	0	0
1 syn	0.51		
1 plane	0.51	0.67	0.77
1 TS1	8.63	10.67	8.65
1 TS2	15.38	13.59	15.38
2 cis	0	2.87	0
2 trans	0.70	0	1.16
2 TS1	10.20	13.89	10.20
2 TS2	17.74	16.31	17.85
3a cis	0	3.33	0.10
3a trans	1.52	0	1.00
3a TS1	12.50	16.33	12.39
3a TS2	19.79	17.99	18.81
3b cis	0.35	3.6	0.49
3b trans	1.26	0.02	1.01
3b TS1	9.48	14.01	10.85
3b TS2	17.06	15.50	15.77
3c cis	0.58	3.1	0
3c trans	0.97	0.45	1.41
3c TS1	10.43	13.56	9.65
3c TS2	17.72	15.91	17.57
4a cis	0	6.21	0
4a trans	1.34	3.15	1.25
4a TS1	12.38	18.84	11.88
4a TS2	19.77	20.68	18.90
4b cis	0.29	6.87	0.79
4b trans	1.04	2.98	1.02
4b TS1	9.06	18.48	11.84
4b TS2	16.40	19.95	16.92
4c cis	3.46	2.66	2.65
4c trans	4.33	0	3.20
4c TS1	12.80	13.11	13.01
4c TS2	19.14	15.46	18.82
5 cis	0	4.40	0
5 trans	0.92	0	0.69
5 TS1	9.37	14.11	9.38
5 TS2	15.67	15.51	16.04
6 cis1	2.65	5.96	2.65
6 cis2	3.20		2.97
6 trans	0.00	0	0
6 TS1	9.83	12.62	9.88
6 TS2	13.38	12.86	13.35

the default value of 4.0 to 2.7 Å^3. The new value seems to be is consistent with the default atomic polarizability parameters for sulfide sulfur (3.0 Å^3) and sulfoxide sulfur (2.7 Å^3). In the following text we refer to this model as MMFF94+ to indicate that we have modified the default MMFF94 parameter set.

Results and Discussion

Conformational aspects for each derivative, **1**−**6**, are discussed in separate sections below. For clarity, the discussion follows the same order in each case: the planarity of the structure, barrier to rotation about the C$_a$−N bond, the relative stability of cis versus trans configurations, and the conformations formed by rotation about the N−C(substituent) bond. Since rotation about the C$_a$−N bond has been a major focus of prior studies, plots of these PESs are not presented here. However, all stable points on these surfaces were optimized, and the geometries and relative energies are discussed. On the other hand, since PESs for rotation about N−C(substituent) bonds have not been reported previously, plots of these PESs are presented for each case.

The data obtained from the MP2/aug-cc-pVDZ (hereafter referred to as MP2) calculations were used to check the performance of the default MMFF94 model. Systematic discrepancies between MMFF94 and MP2 relative energies led to the modification of several torsion and van der Waals parameters, yielding an improved model, MMFF94+. Relative energies for all optimized geometries obtained using different methods are summarized in Table 2. Views of these geometries are provided in the corresponding sections below.
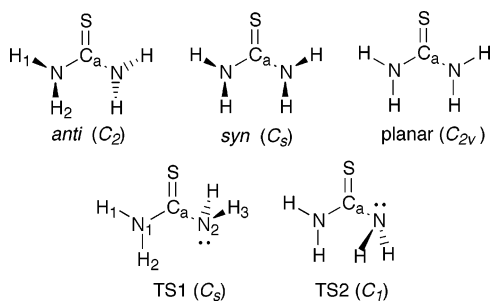
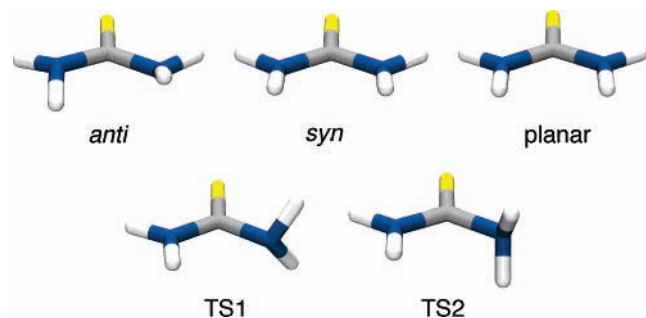**Figure 1.** Five stationary points for thiourea, **1**.

Figure 2. MP2 optimized geometries for **1**.

Thiourea. Prior theoretical studies have identified several stationary points for thiourea, **1**.[16−22] The geometries are defined in Figure 1. Five geometries (one ground state, three transition states, and one second-order saddle point) have been located in the current study, and the MP2 optimized structures are shown in Figure 2. Relative energies are summarized in Table 2.

Considerable effort has been focused on the problem of the planarity of thiourea in the gas phase. Early theoretical calculations[22] and experimental studies of **1** in the solid state[24] predicted a fully planar C_{2v} structure. More recent calculations[16−22] and gas-phase rotational studies[21] on **1** find that the NH_2 groups are slightly out-of-plane. These studies suggested that the lowest energy structure has C_2 symmetry (anti form) and the less stable form has C_s symmetry (syn form). Although the syn form has been found to be a true minimum at the MP2/DZ(d,p)[17] and MP2/6-31++G(d,p)[19] levels, it was characterized as a transition state at the MP2(full)/6-31+G* level (see Supporting Information to ref 20). A planar C_{2v} symmetry structure at the MP2 level has been identified as a second-order stationary point connecting two pairs of syn and anti conformers.[17,20]

In the present study we find that the anti C_2 form is the only minimum on the PES for **1**. The syn C_s form is a transition state for interconverting anti forms, and the planar C_{2v} form is a second-order stationary point with two imaginary frequencies. This result is fully consistent with the fact that the matrix isolated FTIR spectra of thiourea suggests the presence of only one form in the vapor phase.[17] The relative energies of the C_s and C_{2v} states at the MP2 level are very similar, 0.505 and 0.514 kcal/mol, respectively. For comparison, reported relative energies for the C_s and C_{2v} states are 0.09 and 0.09 kcal/mol for HF/6-31G*,[25] 1.50 and 1.08 for MP2/D95**,[18] 1.08 and 1.00 kcal/mol for MP2/6-31G*,[16] 1.23 and 1.01 kcal/mol for MP2-(full)/6-31+G*,[20] and 0.65 and 0.61 kcal/mol for MP2/6-311++G(3df,2pd)//MP4(SDTQ)/6-311++G(3df,2pd).[21] Using the MMFF94 or MMFF94+ models, we could locate the lowest energy anti form and, by enforcing symmetry, the planar C_{2v} form. The relative energy for the C_{2v} isomer is well-reproduced by MMFF94 (0.67 kcal/mol) and MMFF94+ (0.77 kcal/mol). The C_s form could not be located with this model.

TABLE 3: Calculated and Experimental Geometric Parameters for the Anti Conformation of 1^a

feature	MP2	MMFF94	MMFF94+	expt^b
C=S	1.665	1.650	1.650	1.645
C−N	1.375	1.349	1.349	1.368
N−H$_1$	1.012	1.013	1.013	
N−H$_2$	1.014	1.014	1.014	
S−C−N	123.2	122.8	122.9	123.0
N−C−N	113.7	114.3	114.3	
C−N−H$_1$	114.9	116.1	115.8	
C−N−H$_2$	118.5	118.3	117.9	
H$_1$−N−H$_2$	116.0	115.4	115.1	
S−C−N−H$_1$	10.7	8.3	8.3	
S−C−N−H$_2$	154.2	152.0	150.4	
N−C−N−H$_1$	−169.3	−171.7	−171.7	
g	349.5	349.8	348.8	

^{a} Bond lengths in angstroms; angles in degrees. Pyramidalization of the nitrogen is expressed in terms of γ, the sum of the three bond angles subtended at nitrogen. ^{b} Experimental data.[21]

Table 3 summarizes geometrical parameters of the global minimum anti structure of **1**, calculated by various methods, as compared with the available experimental data obtained from gas-phase microwave spectroscopy.[21] All the methods used give structural parameters of similar accuracy when compared with the experimental geometry. The modified parameters in MMFF94+ do not noticeably alter bond lengths but do have a small influence on the bond and dihedral angles. Although the experimental data did not allow a precise determination of the positions of hydrogen atoms, they did indicate that the N−H hydrogen atoms in thiourea lie closer to the NC(=S)N plane than those in urea.[10] This structural feature is reproduced by both electronic structure and molecular mechanics calculations. In both cases, the sum of the three bond angles around the nitrogen (γ(N)) is 7° larger in thiourea than in urea. Note that the decreased nitrogen pyramidalization upon going from urea to thiourea is accompanied by a concomitant shortening of the C_a−N bond (by 0.018 Å at the MP2 level) consistent with a higher rotational barrier about this bond.

Rotation about the C_a−N bond gives rise to a C_s symmetry maximum (TS1) and a C_1 symmetry maximum (TS2), where one nitrogen atom is either almost or exactly planar and the other nitrogen atom changes its hybridization from a mixture of sp^2 and sp^3 at the minima to a sp^3 state at the TS. The two transition states reflect the two possible orientations of the nitrogen lone pair with respect to the C=S bond, with the TS2 state being always higher in energy than TS1.

Rotation around the C_a−N bond breaks the conjugation and significantly destabilizes the corresponding TSs. Loss of the conjugation in TS1 and TS2 should lead to substantial elongation of a one C−N bond and shortening of another. This is reflected in MP2 calculations, but the MMFF94 calculations do not reproduce the bond length changes. For example, MP2 gives long and short lengths of 1.449 and 1.350 Å for TS1, whereas MMFF94 gives values of 1.355 and 1.345 Å.

The relative energies for TS1 and TS2 obtained with MP2 (Table 2) are in agreement with other calculated values of 8.6−10.6 kcal/mol for the lower barrier and 16.0−18.9 kcal/mol for the higher barrier.[20] The barrier height measured in solution, $\Delta G^{\ddagger} = 11.3−13.5$ kcal/mol, is several kilocalories per mole above the calculated values.[25,26] Unfortunately, no experimental values for gas-phase rotational barrier heights have been reported for comparison to the theoretical results. The default MMFF94 model overestimates the barrier height for TS1 and underestimates the barrier height for TS2. This is corrected in MMFF94+.

Methylthiourea. Methylthiourea, **2**, exhibits two nonplanar minima, both in an anti configuration with respect to nitrogen
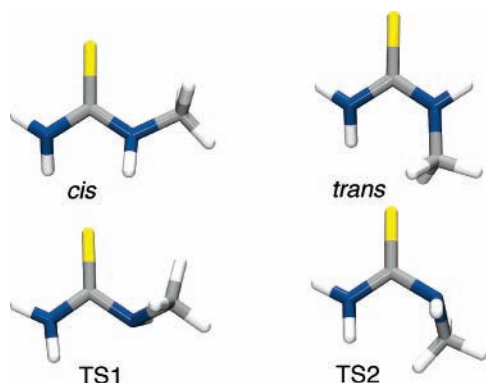
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Figure 3. MP2 optimized geometries for **2**.
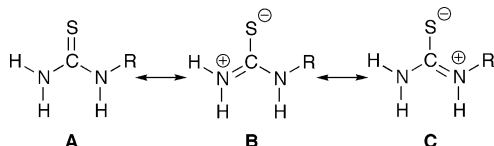
Figure 4. Resonance structures for alkylated thiourea.

TABLE 4: Calculated and Experimental Geometric Parameters for cis 2[a]

feature	MP2	MMFF94	MMFF94+	expt[b]
$C_a=S$	1.669	1.659	1.657	1.688 ± 0.018
C_a-N_1	1.387	1.360	1.358	1.361 ± 0.017
C_a-N_2	1.363	1.366	1.364	1.324 ± 0.013
$C-N_2$	1.456	1.449	1.446	1.453 ± 0.011
N_2-H_3	1.014	1.011	1.011	0.883 ± 0.101
$C-H_4$	1.101	1.093	1.093	
$C-H_5$	1.097	1.093	1.093	0.964 ± 0.039[c]
$C-H_6$	1.098	1.093	1.093	
N_1-C_a-S	122.6	119.8	120.5	119.7 ± 1.5
$N_1-C_a-N_2$	113.8	112.2	112.7	116.5 ± 145
C_a-N_2-C	121.8	124.9	123.1	124.2 ± 1.0
$C_a-N_2-H_3$	117.0	114.7	115.0	117.5 ± 2.7
N_2-C-H_4	111.3	109.1	109.0	
N_2-C-H_5	109.6	110.3	110.1	109.7 ± 2.3[c]
N_2-C-H_6	108.1	108.3	108.4	
$S-C_a-N_2-C$	4.5	4.4	5.0	$0 \pm 3\ (0-11)$[d]
$S-C_a-N_2-H_3$	162.8	159.5	157.7	$180 \pm 6\ (161-180)$[d]
$\gamma(N_1)$	344.7	348.4	347.6	
$\gamma(N_2)$	356.5	355.5	354.5	

[a] Bond lengths in angstroms; angles in degrees. Pyramidalization of the nitrogen is expressed in terms of γ, the sum of the three bond angles subtended at nitrogen. [b] Crystallographic data for 39 thiourea molecules containing at least one $N(H)CH_3$ group in which the methyl substituent is cis to the sulfur atom. [c] Average data for three methyl hydrogen atoms. [d] Dihedral angles range.
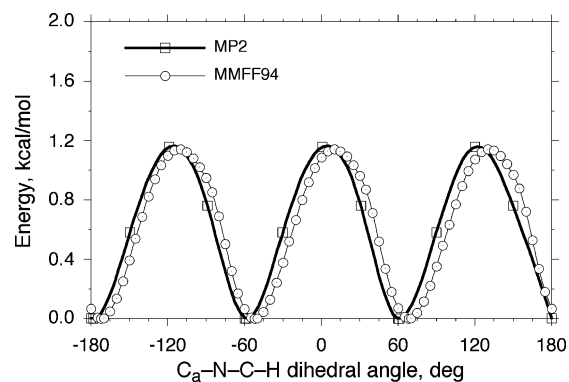

Figure 5. PES for $N-C(sp^3)$ bond rotation in cis **2** at various levels of theory.

pyramidalization. Syn configurations are not stable points on either the MP2 or MMFF94 PES. The two minima, with the methyl group cis and trans to the sulfur,[27] are interconverted by rotation about the C_a-N bond. As with **1**, there are two TS for this interconversion analogous to TS1 and TS2 (see Figure 1). The cis, trans, TS1, and TS2 geometries for **2** have been located in the current study, and MP2 optimized structures are shown in Figure 3. Relative energies are summarized in Table 2.

At the MP2 level, we find the cis form to be the global minimum with the trans form 0.7 kcal/mol higher in energy. Previous electronic structure calculations on **2** reported at the HF/6-31G level gave markedly different results with a global minimum trans form and the cis form 0.7 kcal/mol higher in energy.[28] The difference is likely due to the deficiency of the employed basis set and importance of electron correlation effects required to give the correct energetics and geometry. The default MMFF94 model also predicts a trans global minimum. The smaller sulfur van der Waals radius used in MMFF94+ corrects the discrepancy, which is due to an overestimation of the steric repulsion between the large sulfur atom and the methyl group in the cis form.

NMR[29,30] and Raman[28] spectra of **2** in solution show the coexistence of both cis and trans isomers. This result is consistent with the small energy difference between the cis and trans rotamers of **2**. On the other hand, the spectral and X-ray diffraction analysis of **2** in the solid state, which is strongly influenced by intermolecular hydrogen bonding, shows that only the trans conformation is present.[28]

N-Methyl substitution in thiourea increases the relative energy of TS1 by 1.57, 3.22, and 1.55 kcal/mol with MP2, MFF94, and MMFF94+ methods, respectively (Table 2). Although steric effects on rotational barriers cannot be completely ruled out,[25] this increase in barriers can be rationalized on consideration of thiourea resonance structures A–C shown in Figure 4. Contribution from resonance structure C is expected to increase when R is an electron-donating group. This should result in an increase of the π-bonding character of the $C_a-NH(CH_3)$ bond and in a decrease of the C_a-NH_2 bond order. Experimental barriers for these rotations are available for **2** only in solution,[26,29] which are consistently higher than calculated ones. Nevertheless, in accord with the classical resonance model, they are higher for rotation around the $C-NH(CH_3)$ bond ($\Delta G^{\ddagger} = 15.1$ kcal/mol)

and lower for rotation around the $C-NH_2$ bond ($\Delta G^{\ddagger} = 10.2$ kcal/mol) as compared with the rotational barrier for **1** ($\Delta G^{\ddagger} = 11.3$ kcal/mol).[29]

Table 4 summarizes the geometric parameters of the global minimum cis **2**, calculated by various methods. Although experimental gas-phase structural data for **2** are not available, experimental averages from X-ray diffraction data for 39 cis methylthiourea derivatives are used for comparison with theoretical results. As with **1**, the agreement with the experimental data is good. The average deviation from X-ray bond lengths (heavy atoms) and angles are as follows: MP2, 0.022 Å, 2.7°; MMFF94, 0.019 Å, 1.7°; MMFF94+, 0.020 Å, 1.9°.

Introduction of the weak electron-donating methyl group to **1** results in a slight increase of the $C_a=O$ and C_a-N_1 bond lengths and in a small decrease of the C_a-N_2 bond length at the MP2 level, as predicted by resonance considerations (see C in Figure 4). Note that the sum of the three bond angles (γ-(N_2)) around the methylated nitrogen is 7–12° larger than that for the NH_2 group ($\gamma(N_2)$). The relative flattening of $O=C_a-N_2-C$ and $O=C_a-N_2-H_3$ dihedral angles is also indicative of reduced pyramidalization at the methylated nitrogen.

Figure 5 shows the PESs for the rotation of the methyl group in cis **2** at MP2 and MMFF94+ levels of theory. These methods
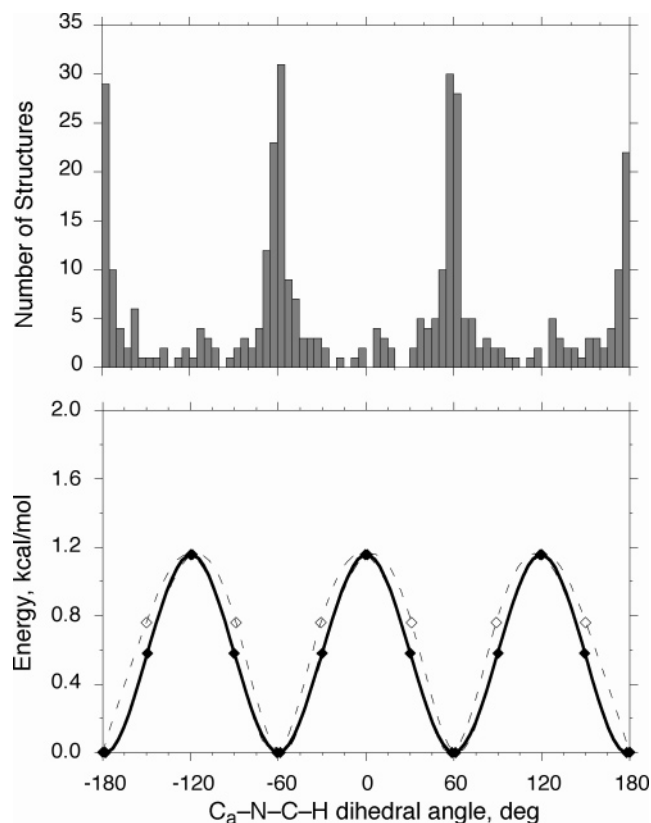
Figure 6. Comparison of the distribution of C_a–N–C–H dihedral angles observed in crystal structures with an MP2 PES (bold line) derived by combining the PESs for the two enantiomers of cis **2** (dashed lines).

yield three equivalent minima and maxima, though the position of the stationary points on the PES are slightly different. The MP2 equilibrium structure (178°) is closer to an ideal staggered conformation (180°) than those obtained from MMFF94+ (172°) calculations (values of one of the H–C–N–C_a dihedral angles are given in parentheses). The barrier to rotation of the CH_3 group is close to 1.2 kcal/mol with both methods.

Figure 6 illustrates the distribution of C_a–N–C–H dihedral angles in crystal structures, plotted as a histogram of the number of occurrences versus the values of dihedral angles. One comment should be made before comparison between theory and experiment. The three-dimensional structure of the anti configuration implies the existence of a pair of enantiomers with opposite orientation of pyramidal nitrogen atoms. The PESs for one stereoisomer are shown in Figure 5. The corresponding PESs for the other stereoisomer are equal to the reflection of the PESs shown in Figure 5 through 0°. Experimental structures, due to rapid pyramidal inversion, reflect time-averaged atomic positions. Thus, the structures often appear planar, and it is not possible to assign chirality to them. To provide a meaningful comparison with experiment, we have combined the PESs for the two enantiomers to yield a PES in which every point on the surface corresponds to the lower of the two energies for the enantiomers, as shown in Figure 6. Consistent with theoretical results, the experimental data show that the dihedral angle is populated predominantly in the −60 ± 20, 60 ± 20, and 180 ± 20° regions, where the calculated energies are within 0.4 kcal/mol from the minima.

Ethylthiourea. Ethylthiourea, **3**, behavior is similar to that observed in **2**. All minima adopt an anti configuration with respect to nitrogen pyramidalization. Rotation about the N–C(ethyl) bond gives rise to three minima for the cis form and three
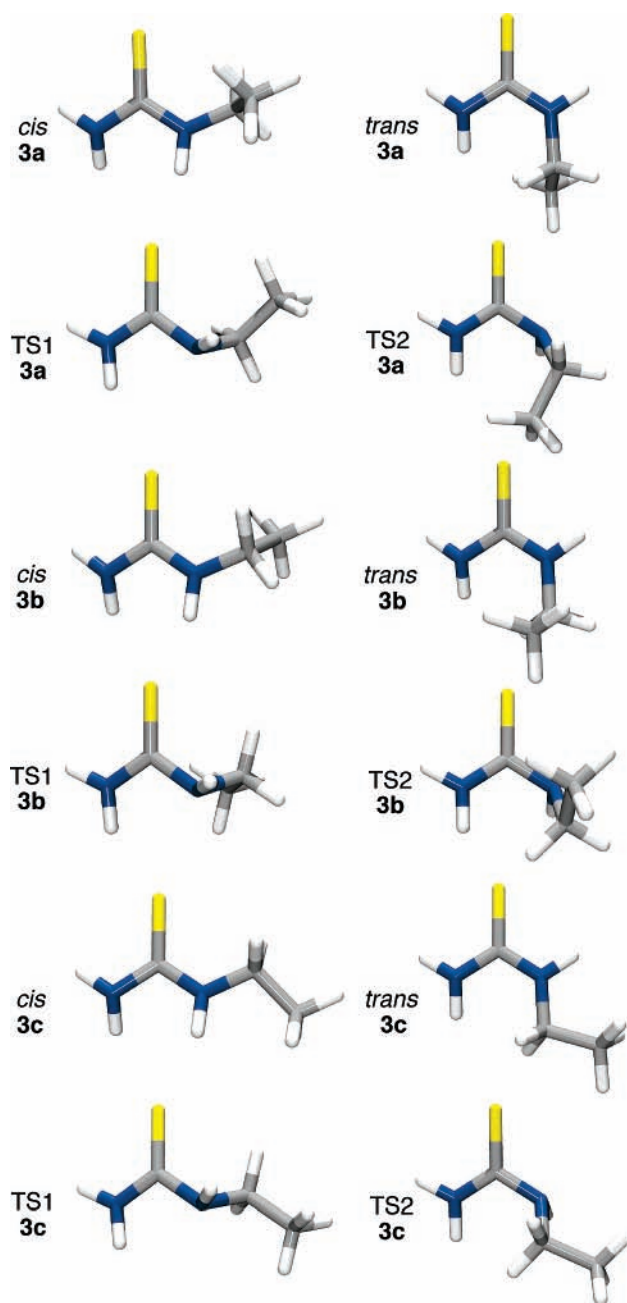

Figure 7. MP2 optimized geometries for **3**.

minima for the trans form. For a given ethyl rotamer, the cis and trans forms are interconverted by rotation about the C_a–N bond with two possible transition states. Three cis minima, three trans minima, three TS1, and three TS2 geometries for **3** have been located in the current study, and MP2 optimized structures are shown in Figure 7. Relative energies are summarized in Table 2.

At the MP2 level for each ethyl rotamer, the cis form is more stable than the corresponding trans form. The relative energies of the trans forms are 1.52, 0.91, and 0.39 kcal/mol for **3a**−**c**, respectively. By contrast, the relative stability of cis forms is greatly underestimated at the MMFF94 level. The problem is fixed in MMFF94+. The relatively small energy difference between the lowest energy cis and trans forms (0.97 kcal/mol) is consistent with the presence of two rotational isomers in solution, as follows from two CH_2 signals on the ^{1}H NMR spectrum of ethylthiourea cadmium(II) complex[6c] and two ν-(C=S) bands in Raman spectra of **2** associated with the cis and

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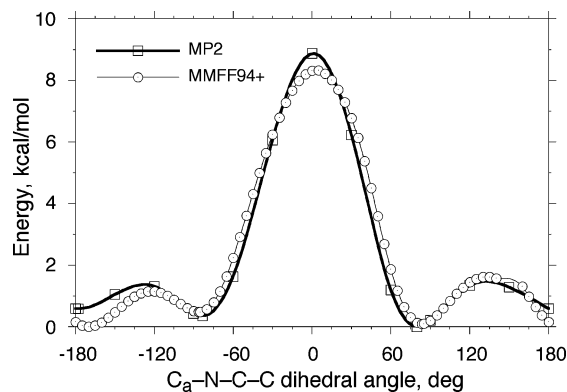*J. Phys. Chem. A, Vol. 110, No. 14, 2006* **4683**

Figure 8. PES for N−C(alkyl) bond rotation in cis **3** at various levels of theory.

trans rotamers.[27] Analysis of the CSD shows that primary alkyl substituents, -CH_2CH_{2-}X, adopt a cis configuration in 187 of the 241 examples.

The relative energy of the three possible forms of TS1 ranges from 9.5 to 12.5 kcal/mol with MP2. The overestimated range of 13.5−16.3 kcal/mol with MMFF94 is corrected to a range of 9.7−12.4 kcal/mol with MMFF94+. The lower values of barrier heights, which are similar to those obtained for **2**, reflect electronic (inductive) effects of the attached alkyl group. A comparison of the geometric parameters for **3** at various levels of theory show the same behavior as previously described for **2**.

Figure 8 shows the PESs for rotation of the ethyl group in cis **3** at MP2 and MMFF94+ levels of theory. The MP2 and MMFF94+ PESs are very similar. Both methods yield three minima located near ±80°, **3a** and **3b**, and −174°, **3c**. The MP2 barrier heights are 8.9 kcal/mol near 0°, 1.5 kcal/mol near 135°, and 1.4 kcal/mol at −125°. The asymmetric profile of the PES results from the pyramidal nitrogen atoms. The global minimum near 80°, **3a**, corresponds to a geometry in which the CH_2CH_3 group is staggered with respect to the N−H bond; in other words, where one of the H−C−N−H dihedral angles is near 60° (44° with both MP2 and MMFF94+). The minimum near −80°, **3b**, is less stable, due to the fact that one of the C−H bonds and the N−H bond adopt a partially eclipsed conformation (H−C−N−H dihedral angles of −17 and −16° with MP2 and MMFF94, respectively).

X-ray data for 187 examples of cis CH_2CH_2X substituents (X is any arbitrary group) on thiourea provides an experimental view of the C_a−N−C−C dihedral angle distribution. This distribution is shown in Figure 9, where it is compared with the MP2 PESs for the two enantiomers of cis **3** (see discussion of **2**). In agreement with the theoretical results, the C_a−N−C−C dihedral angle is populated predominantly in the regions near the calculated minima at ±(90 ± 30°) and 180 ± 30°.

Isopropylthiourea. Isopropylthiourea, **4**, behavior is analogous to that observed for the ethyl derivative, **3**. All minima adopt an anti configuration with respect to nitrogen pyramidalization. Rotation about the N−C(ethyl) bond gives rise to three minima for the cis form and three minima for the trans form. For a given isopropyl rotamer, the cis and trans forms are interconverted by rotation about the C_a−N bond with two possible transition states. Three cis minima, three trans minima, three TS1, and three TS2 geometries for **4** have been located in the current study, and MP2-optimized structures are shown in Figure 10. Relative energies are summarized in Table 2.

At the MP2 level for each isopropyl rotamer, the cis form is more stable than the corresponding trans form. The relative
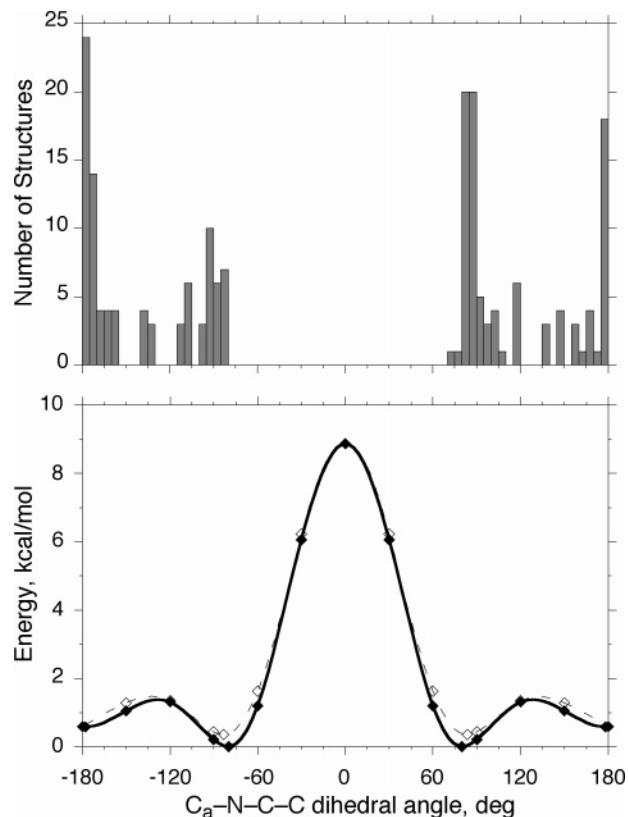

Figure 9. Comparison of the distribution of C_a−N−C−C dihedral angles observed in crystal structures with an MP2 PES (bold line) derived by combining the PESs for the two enantiomers of cis **3** (dashed lines).

energies of the trans forms are 1.34, 0.75, and 0.87 kcal/mol for **4a**−**c**, respectively. By contrast, the relative stability of the cis forms is greatly underestimated at the MMFF94 level. The problem is fixed in MMFF94+. To our knowledge, no experimental data on conformational preferences in the gas phase or in solution have yet been reported for isopropylthiourea derivatives. The structural information in the solid state is mainly available for N,N′-diisopropylthiourea that adopts cis−trans conformation.[31]

Barriers to rotation about the C_a−N bond are dependent on the isopropyl group position. They range from 9.1 to 12.8 kcal/mol with MP2, from 13.8 to 18.8 kcal/mol with MMFF94, and from 11.8 to 13.1 kcal/mol with MMFF94+. A comparison of the geometric parameters for **4** at various levels of theory yields the same behavior as previously described for **2** and **3**.

Figure 11 shows the PESs for rotation of the isopropyl group in cis **4** at different levels of theory. Here, for reasons of symmetry, the C_a−N−C−H dihedral angle is plotted on the x-axis. All calculations yield two minima near ±40°, **4a** and **4b**, separated by a comparatively low-energy barrier near 0°, and one high-energy minimum near 180°, **4c**, separated from the other ones by high-energy barriers near ±120°. As with **3**, the MP2 and MMFF94+ methods give very similar PESs. The maximum deviation between MP2 and MMFF94+ methods is 0.8 kcal/mol at 180°. The global minimum near −40°, **4a**, corresponds to a rotamer where the isopropyl group is staggered with respect to the N−H bond. The local minimum near 40°, **4b**, corresponds to a rotamer where one of the C−C bonds of the isopropyl group is eclipsed with respect to the N−H bond (H−N−C−C dihedral angle of −16° with both MP2 and MMFF94).
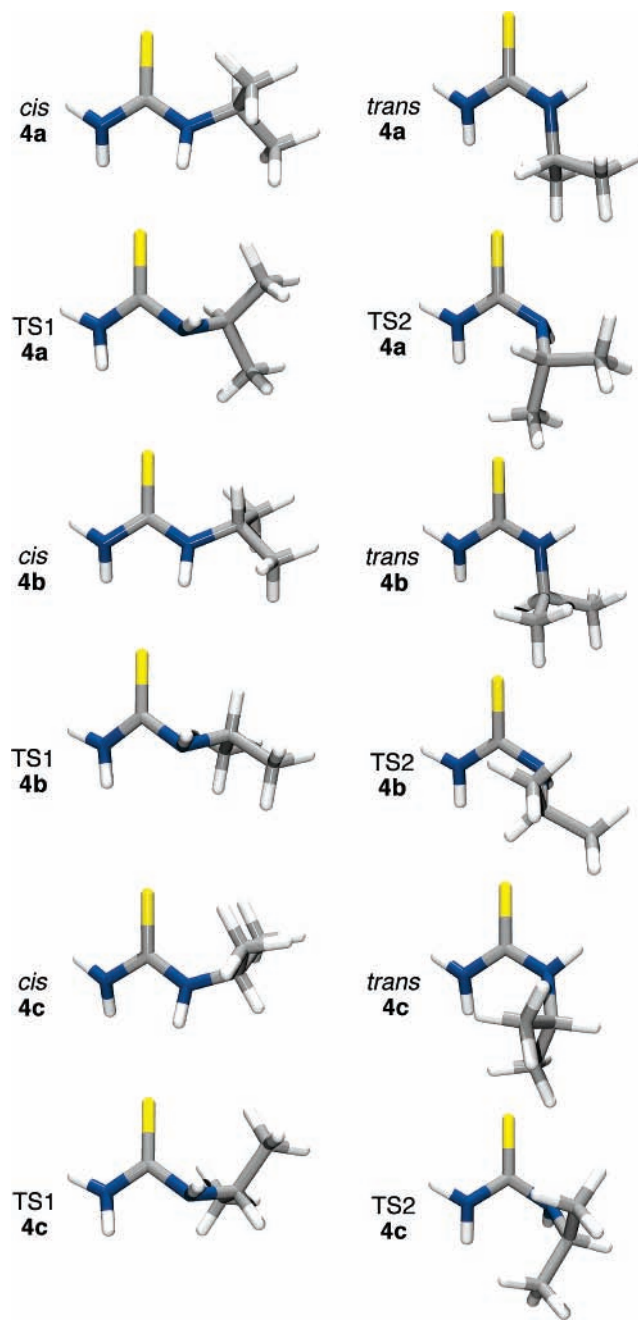
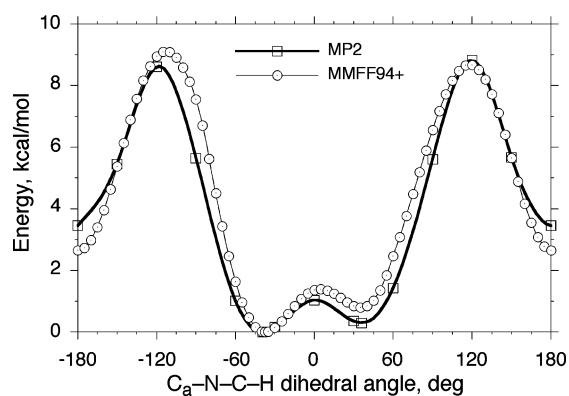**Figure 10.** MP2 optimized geometries for **4**.

Figure 11. PES for N−C(alkyl) bond rotation in cis **4** at various levels of theory.

X-ray data for 12 examples of thiourea derivatives bearing secondary alkyl substituents in the cis configuration illustrate
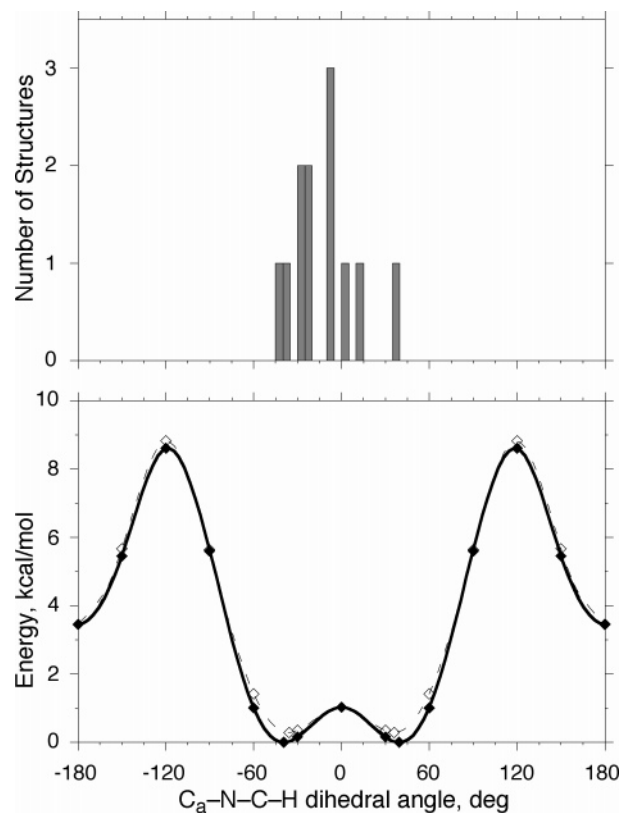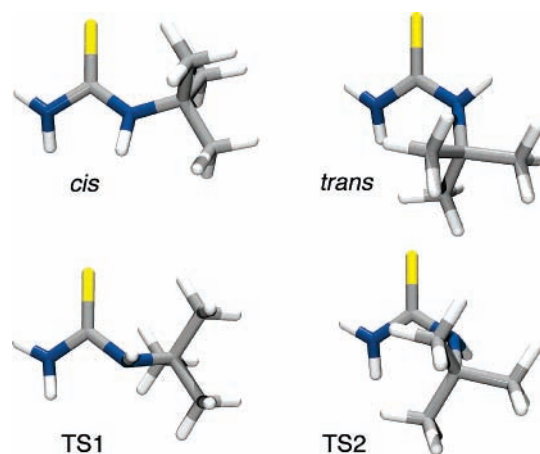

Figure 12. Comparison of the distribution of C_a−N−C−H dihedral angles observed in crystal structures with an MP2 PES (bold line) derived by combining the PESs for the two enantiomers of cis **4** (dashed lines).

Figure 13. MP2 optimized geometries for **5**.

the experimental distribution of the C_a−N−C−H angles. This distribution is shown in Figure 12, where it is compared with the MP2 PESs for the two enantiomers of cis **4** (see discussion of **2**). The theoretical results are fully consistent with the experimental distribution. The dihedral angle is populated only in the region of ±45° between high-energy barriers. The higher energy minimum, with a C_a−N−C−H dihedral angle of 180°, has not been experimentally observed.

***tert*-Butylthiourea.** *tert*-Butylthiourea, **5**, exhibits one cis minimum and one trans minimum, both in the anti configuration with respect to nitrogen pyramidalization. The cis and trans minima, TS1, and TS2 geometries for **5** have been located in the current study, and MP2 optimized structures are shown in Figure 13. Relative energies are summarized in Table 2.
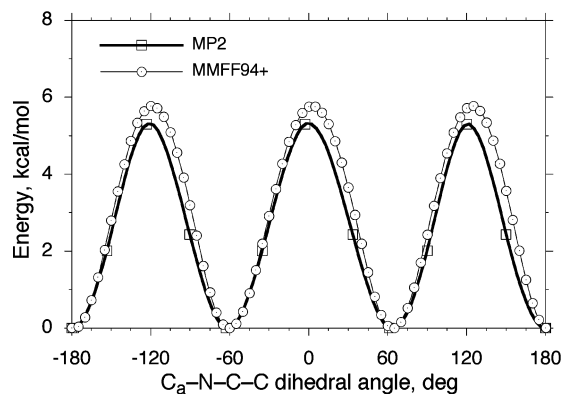
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Figure 14. PES for N−C(alkyl) bond rotation in cis **5** at various levels of theory.

As with other alkyl-substituted thioureas, the cis form is the global minimum at the MP2 level. The cis/trans energy difference is 0.92 kcal/mol. As before, energetic discrepancies with the default MMFF94 model are greatly diminished with MMFF94+. Examination of the CSD shows that *tert*-butyl derivatives of thiourea adopt the cis configuration in five of the six examples. The barrier to rotation about the C_a−N bond in **5**, 9.4 kcal/mol with MP2, is similar to those obtained for **2**−**4**, 9.1−10.3 kcal/mol, at the same level of theory.

Figure 14 shows the PESs for rotation of the *tert*-butyl group in cis **5** at different levels of theory. Both methods yield 3-fold rotational potentials where the minima occur with methyl groups staggered with respect to the C_a−N bond. Three structurally identical minima are located at ±60 and 180°. The barriers to rotation of the *tert*-butyl group are 5.3 and 5.8 kcal/mol with MP2 and MMFF94+, respectively.

X-ray data for thiourea derivatives bearing tertiary alkyl substituents in the cis configuration illustrate the experimental distribution of the C_a−N−C−C angles. This distribution is shown in Figure 15, where it is compared with the MP2 PESs for the two enantiomers of cis **5** (see discussion of **2**). The theoretical results are fully consistent with the experimental distribution. The dihedral angle is populated at the predicted minima of ±60 and 180°.

Phenylthiourea. Phenylthiourea, **6**, exhibits two cis minima and one trans minimum. The trans minimum and a high-lying cis minimum have a syn configuration while the lowest energy cis minimum has an anti configuration, with respect to nitrogen pyramidalization. These three minima, TS1, and TS2 geometries for **6** have been located in the current study and MP2 optimized structures are shown in Figure 16. Relative energies are summarized in Table 2.

In contrast to alkyl-substituted thioureas, the trans form is significantly more stable than either cis form. The relative energy of the most stable cis isomer is 2.65 kcal/mol with the MP2 and MMFF94+ methods. This result is consistent with an NMR spectroscopic study of phenylthiourea cadmium(II) complex that shows only the trans form is present in solution.[6c] In addition, **6** adopts a trans form in the solid state.[32] Barriers to rotation about the C_a−N bond are 9.83 and 9.88 kcal/mol with MP2 and MMFF94+, respectively.

A detailed comparison of the geometric parameters at various levels of theory was performed (table provided as Supporting Information). Bond lengths and valence angles pertaining to the thiourea fragment are compared with experimental averages from X-ray diffraction data for the trans and cis forms of **6** that are not coordinated with metals through the sulfur atom. The average absolute deviations for bond lengths (heavy atoms) and
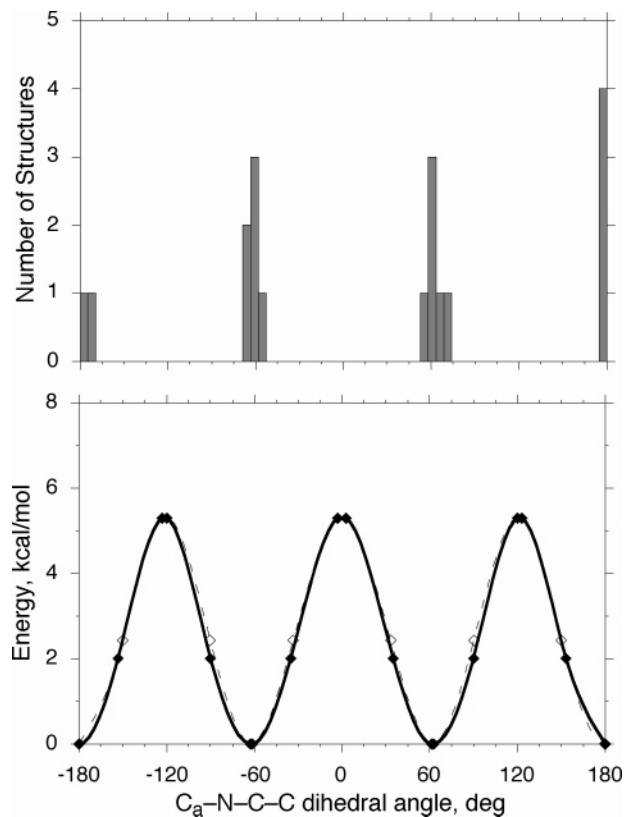

Figure 15. Comparison of the distribution of C_a−N−C−C dihedral angles observed in crystal structures with an MP2 PES (bold line) derived by combining the PESs for the two enantiomers of cis **5** (dashed lines).
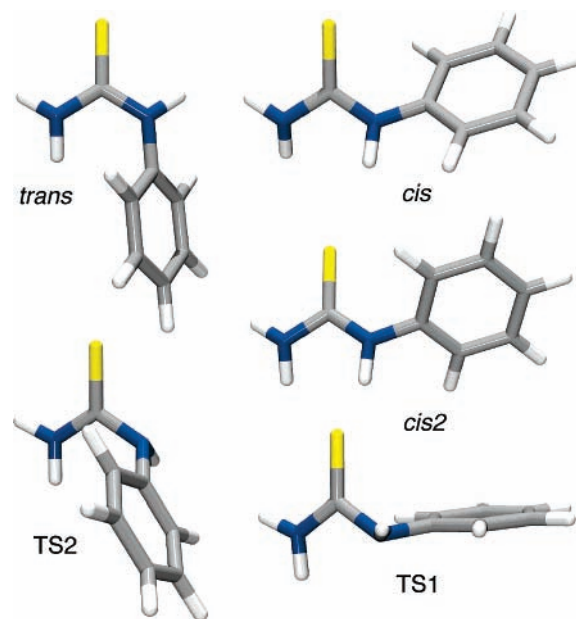

Figure 16. MP2 optimized geometries for **6**.

bond angles are as follows: MP2, 0.020 Å, 2.7°; MMFF94, 0.014 Å, 3.2°; and MMFF94+, 0.014 Å, 1.4° for the trans form and MP2, 0.018 Å, 2.2°; MMFF94, 0.016 Å, 2.9°; and MMFF94+, 0.015 Å, 1.7° for the cis form.

Figure 17 shows the PESs for rotation of the phenyl group in cis **6** at different levels of theory. In contrast to previous results for urea the MP2 calculations yield an energy profile with two different minima located at C_a−N−C−C dihedral angles of −55 and −131°. The energy difference between these
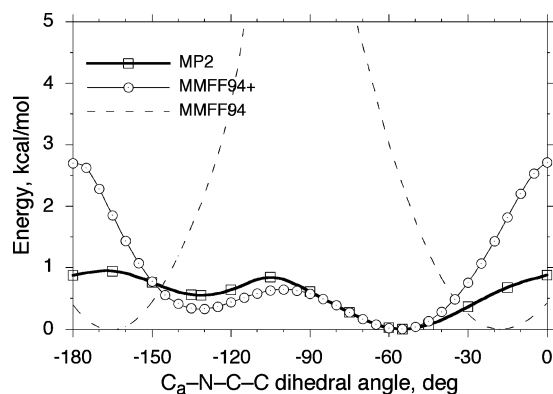
Figure 17. PES for N−C(aryl) bond rotation in cis **6** at various levels of theory.

minima is 0.55 kcal/mol. Maxima occur near −110 and −165° with the barrier heights of 0.95 and 0.86 kcal/mol, respectively. Comparison of the PES obtained from default MMFF94 versus that obtained at the MP2 level revealed poor agreement. The default MMFF94 model, as in the case of phenylurea,[10] yields a very high barrier for rotation of the phenyl group (almost 10 kcal/mol). In a prior study, generalized MMFF94 parameters for two torsional interactions, H−N−C(aryl)−C(aryl) and C_a−N−C(aryl)−C(aryl), were modified to reproduce the MP2 barrier height and position of the minimum for phenylurea.[10] The use of these parameters along with other modifications (see Theoretical Details) satisfactorily reproduces the low-energy regions of the MP2 PES for **6**, although the barrier near 0° is overestimated.

X-ray data for phenyl-substituted thiourea derivatives in the cis configuration illustrate the experimental distribution of the C_a−N−C−C angles. This distribution is shown in Figure 18, where it is compared with the MP2 PESs for the two enantiomers of cis **6** (see discussion of **2**). Since the barrier for rotation of the phenyl group is relatively small (<1 kcal/mol), the dihedral angle adopts values ranging from −180 to 0°.

Conformational Behavior of Thiourea versus Urea. Prior electronic structure calculations using high-level methods indicate that C_a−N partial double bond character increases on going from urea to thiourea.[20] This observation is supported by the C_a−N rotational barriers, N-inversion barriers, charge distributions, and electron occupancies of the lone pair on nitrogen, etc. Analogous effects are observed on going from amides to thioamides.[20,33] At the MP2 level of theory employed in this study, comparison of results for thiourea, **1**, with those obtained for urea[10] are fully consistent with this observation. On going from urea to **1**, the C_a−N bonds become shorter (from 1.395 to 1.375 Å), the nitrogen becomes more planar (γ from 343.2 to 349.5°), and the barrier of rotation increases (from 8.16 to 8.63 kcal/mol). The same effects are seen on comparing urea analogues with **2**−**6**, where the average increase in C_a−N rotational barrier is 0.70 kcal/mol. Structural changes resulting from the partial double bond character of the C_a−N bond are small and do not account for differences in the relative energy of N-substituted thiourea minima versus those of N-substituted ureas.

One significant difference between urea and thiourea derivatives is the relative stability of their cis versus trans conformations.[27] As summarized in Table 5, the alkyl-substituted derivatives **2**−**5** and their urea counterparts all prefer a cis configuration. The energy difference between the two forms, however, is greater for urea than thiourea. As a consequence, trans forms of alkylated ureas are less likely to be populated
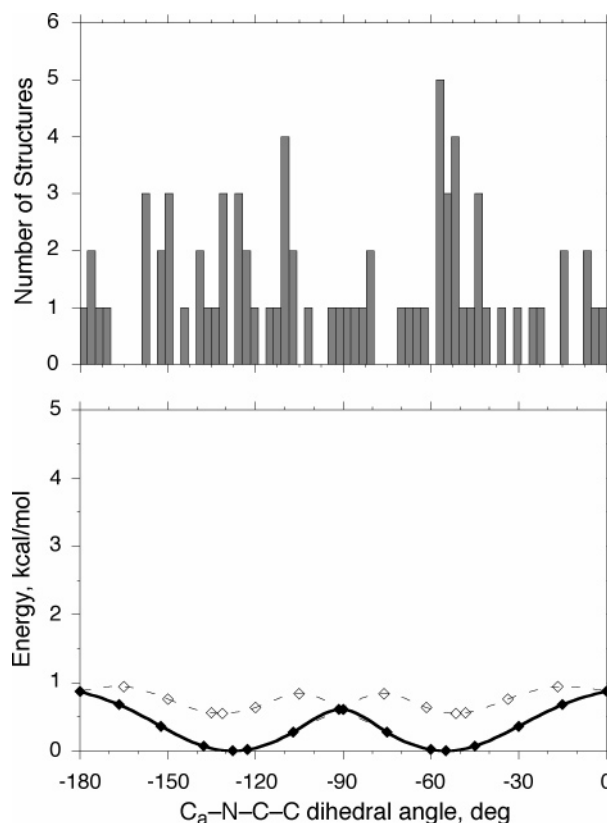

Figure 18. Comparison of the distribution of C_a−N−C−C dihedral angles observed in crystal structures with an MP2 PES (bold line) derived by combining the PESs for the two enantiomers of cis **6** (dashed lines).

TABLE 5: Comparison of the Relative Stabilities (kcal/mol) of cis and trans Forms for N-Substituted Urea and Thiourea Derivatives at the MP2 Level of Theory[a]

substituent	cis urea	trans urea	cis thiourea	trans thiourea
methyl (**2**)	0	1.25	0	0.75
ethyl (**3**)	0	0.95	0	0.45
isopropyl (**4**)	0	1.29	0	1.04
tert-butyl (**5**)	0	2.61	0	0.92
phenyl (**6**)	0.94	0	2.65	0

[a] Urea data are taken from ref 10. In cases where there are more than one minimum, such as **3**, **4**, and **6**, the energy of the most stable form is given.

than those of N-alkylated thioureas. This observation is consistent with crystal structures, showing that N,N′-dialkylureas form hydrogen bonding networks in the cis−cis form only, whereas N,N′-dialkylthioureas form hydrogen bonding networks with both the cis−cis and cis−trans forms.[34] The behavior is rationalized by increased steric hindrance in the cis form that results when the smaller oxygen atom is replaced with the larger sulfur atom. The increased steric bulk of sulfur also explains the behavior of the phenyl-substituted derivative, **6**. Here although both urea and thiourea prefer a trans configuration, the cis form is 2.65 kcal/mol higher in energy in thiourea, but only 0.94 kcal/mol higher in energy for urea. Thus, the cis form of phenylurea is significantly more likely to be populated than that of phenylthiourea.

Comparison of the PESs for N−C(alkyl) rotation in cis forms of **2**−**5** to those observed for urea derivatives[10] reveals that they have very similar shapes with minima occurring in the same locations irrespective of O or S substitution. Consistent with the larger size of sulfur, the barriers to rotation in thiourea, which correspond to eclipsed conformations with respect to the C=S

bond, are 15−30% higher than those in the corresponding urea. In contrast, the PES for N−C(arene) rotation in cis **6** is much different from that seen in phenylurea. As a consequence of the strong steric repulsion between sulfur and the ortho-hydrogen of the phenyl group, the angle between the thiourea and phenyl planes is −55°, whereas the same angle for phenylurea is −21°. Very similar values were observed in a comparative crystal structure analysis of *N*-phenylurea and *N*-phenylthiourea derivatives.[35] The structures indicate that there is less conjugation in **6** than in phenylurea. Loss of conjugation would lead to a destabilization of the ground state, providing an explanation for the fact that, unlike the alkyl-substituted cases **2**−**5**, the barrier to rotation in **6** (0.95 kcal/mol) is actually lower than that in phenylurea (2.4 kcal/mol).

Conclusions

Exhaustive conformational analyses of thiourea, **1**, methylthiourea, **2**, ethylthiourea, **3**, isopropylthiourea, **4**, *tert*-butylthiourea, **5**, and phenylthiourea, **6**, have been performed with respect to nitrogen pyramidalization and rotation about both C_a−N and N−C(substituent) bonds at the MP2/aug-ccpVDZ level of theory. Fully optimized geometries are in agreement with available experimental data. In addition, PESs for N−C(substituent) rotation are consistent with the experimental dihedral angle distributions observed in X-ray crystal structures.

The results of electronic structure calculations establish that the equilibrium conformation for thiourea, **1**, and monoalkylthioureas, **2**−**5**, is the anti form. The syn form is not a stationary point on the PESs for **2**−**5**, while it is a transition state for the conversion between the two equilibrium anti forms for **1**. In **2**−**5**, the cis configurations are more stable than the trans configurations. The default MMFF94 model greatly underestimates the relative stability of the cis form and fails to reproduce the relative stability order for the cis/trans forms. Rotational barriers around C_a−N bond for different alkyl substituents vary slightly at the MP2 level (8.6−9.4 kcal/mol). Corresponding barrier heights calculated by the MMFF94 force field (13.1−14.1 kcal/mol) were systematically greater than those obtained with the MP2 method.

Conformational preferences in **6** are different from those in **2**−**5**. At the MP2 level, the trans isomer in the syn form is predicted to be the global minimum, 2.7 kcal/mol more stable than the cis isomer in the anti form. In addition, a secondary cis minimum adopting a syn conformation was located. The default MMFF94 force field predicts the trans form to be 6.0 kcal/mol lower than the cis form and yields a very high barrier, about 10 kcal/mol, for rotation of the phenyl group as compared with the corresponding MP2 barrier that is less than 1 kcal/mol.

We find that the default MMFF94 does a good job at predicting the structures of thiourea derivatives, **1**−**5**. In addition, with the exception of **6**, examination of PESs for rotation about N−C(substituent) bonds reveals a good correspondence between MMFF94 and MP2 PESs with regard to both relative energies on the PES and the position of minima and maxima. The MMFF94 model fails, however, to reproduce C_a−N rotational barriers and the relative energies of cis and trans forms. It also greatly overestimates the N−C(aryl) rotational barrier. On examination of the default parameter set, these failures were traced to the use of generic torsion parameters and an unusually large van der Waals radius for the thiocarbonyl sulfur. Marked improvement in agreement with the relative energies from MP2 was obtained after simple modification to selected torsion parameters and one of the van

der Waals parameters for sulfur. The modified model, MMFF94+, in the majority of cases reproduces MP2 barrier heights for rotation about the C_a−N bond, relative energies of cis and trans forms, and rotational PESs for **2**−**6** to within ≤1 kcal/mol.

The conformational differences between urea and thiourea groups have some important consequences in anion receptor design. Because thiourea N−H groups are more acidic than urea N−H groups, it is expected that hosts containing thiourea functional groups will form stronger complexes than their urea-containing counterparts, provided they do not undergo deprotonation.[8u] In most hosts that contain urea[36] or thiourea functionality,[8] the group is normally N,N′-disubstituted and the intent is that it will chelate the anion through both N−H donor groups. This requires that the functional group adopt a cis−cis form. Although this form will be preferred by both *N,N′*-dialkylated urea and thiourea derivatives, urea molecules will be more preorganized for anion chelation than thiourea ones. Moreover, when one of the substituents is a phenyl group, the resulting structures will prefer a configuration in which the phenyl group is trans to the C=X bond, resulting in a cis−trans form. Reorganization to generate the cis−cis form required for chelation is energetically more favorable for urea than for thiourea.

Thus, seeking to enhance anion binding by converting urea groups to the more acidic thiourea groups may be off-set by a decrease in the degree of preorganization of the host molecule.

Supporting Information Available: Cartesian coordinates and energies (hartrees) for the MP2/aug-cc-pVDZ optimized equilibrium and transition-state geometries and a table comparing calculated geometric data for **6** to that observed in X-ray crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Ren, J. S.; Diprose, J.; Warren, J.; Esnouf, R. M.; Bird, L. E.; Ikemizu, S.; Slater, M.; Milton, J.; Balzarini, J.; Stuart, D. I.; Stammers, D. K. *J. Biol. Chem.* **2000**, *275*, 5633. (b) Venkatachalam, T. K.; Sudbeck, E. A.; Mao, C.; Uckun, F. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 523. (c) Onderwater, R. C. A.; Commandeur, J. N. M.; Vermeulen, N. P. E. *Toxicology* **2004**, *197*, 81. (d) Venkatachalam, T. K.; Uckun, F. M. *Synth. Commun.* **2005**, *35*, 2039.

(2) Rodriguez-Fernandez, E.; Manzano, J. L.; Benito, J. J.; Hermosa, R.; Monte, E.; Criado, J. J. *J. Inorg. Biochem.* **2005**, *99*, 1558, and references therein.

(3) (a) Pluta, T.; Sadlej, A. J. *J. Chem. Phys.* **2001**, *114*, 136. (b) Zhou, W. Q.; Lu, R. D.; Wang, X. *J. Mol. Struct. (THEOCHEM)* **2003**, *624*, 123.

(4) (a) Stankovic, Z. D.; Vukovic, M. *Electrochim. Acta* **1996**, *41*, 2529. (b) Bolzan, A. E.; Haseeb, A. S. M. A.; Schilardi, P. L.; Piatti, R. C. V.; Salvarezza, R. C.; Arvia, A. J. *J. Electroanal. Chem.* **2001**, *500*, 533. (c) Gassa, L. M.; Lambi, J. N.; Bolzan, A. E.; Arvia, A. J. *J. Electroanal. Chem.* **2002**, *527*, 71. (d) Quraishi, M. A.; Ansari, F. A.; Jamal, D. *Mater. Chem. Phys.* **2002**, *77*, 687.

(5) (a) Trochimczuk, A. W. *Eur. Polym. J.* **1998**, *34*, 1657. (b) Trochimczuk, A. W.; Kolarz, B. N. *Eur. Polym. J.* **2000**, *36*, 2359.

(6) (a) Perez-Marin, L.; Castro, M.; Otazo-Sanchez, E.; Cisneros, G. A. *Int. J. Quantum Chem.* **2000**, *80*, 609. (b) Gambino, D.; Kremer, E.;

Baran, E. J. *Spectrochim. Acta* **2002**, *58*, 3085. (c) Moloto, M. J.; Malik, M. A.; O'Brien, P. Motevalli, M. Kolawole, G. A. *Polyhedron* **2003**, *22*, 595. (d) Castro, M.; Cruz, J.; Otazo-Sanchez, E.; Perez-Marin, L. *J. Phys. Chem. A* **2003**, *107*, 9000.

(7) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196. (b) Kasmi, S.; Hamelin, J.; Benhaoua, H. *Tetrahedron Lett.* **1998**, *39*, 8093. (c) Boga, C.; Forlani, L.; Silvestroni, C.; Corradi, A. B.; Sagarabotto, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1363. (d) Anshu, D.; Kapil, A.; Meha. S. *Synth. Commun.* **2004**, *34*, 1141. (e) Heinelt, U.; Schultheis, D.; Jager, S.; Lindenmaier, M.; Pollex, A.; Beckmann, H. S. G. *Tetrahedron* **2004**, *60*, 9883.

(8) (a) Buhlmann, P.; Nishizawa, S.; Xiao, K. P.; Umezawa, Y. *Tetrahedron* **1997**, *53*, 1647. (b) Sasaki, S.; Mizuno, M.; Naemura, K.; Tobe, Y. *J. Org. Chem.* **2000**, *65*, 275. (c) Benito, J. M.; Gomez-Garcia, M.; Jimenez Blanco, J. L.; Ortiz Mellet, C.; Garcia Fernandez, J. M. *J. Org. Chem.* **2001**, *66*, 1366. (d) Sasaki, S.; Citterio, D.; Ozawa, S.; Suzuki, K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2309. (e) Herges, R.; Dikmans, A.; Jana, U.; Kohler, F.; Jones, P. G.; Dix, I.; Fricke, T.; Konig, B. *Eur. J. Org. Chem.* **2002**, *3004*. (f) Lee, D. H.; Im, J. H.; Lee, J.-H.; Hong, J.-I. *Tetrahedron Lett.* **2002**, *43*, 9637. (g) Kondo, S.; Nagamine, M.; Yano, Y. *Tetrahedron Lett.* **2003**, *44*, 8801. (h) Tumcharem, G.; Tuntulani, T.; Coles, S. J.; Hursthouse, M. B.; Kilburn, J. D. *Org. Lett.* **2003**, *5*, 4971. (i) Nie, L.; Li, Z.; Zhang, X.; Yang, R.; Liu, W.-X.; Wu, F.-Y.; Xie, J.-W.; Zhao, Y.-F.; Jiang, Y.-B. *J. Org. Chem.* **2004**, *69*, 6449. (j) Zeng, Z.-Y.; He, Y.-B.; Wei, L.-H.; Wu, J. L.; Huang, Y.-Y.; Meng, L.-Z. *Can. J. Chem.* **2004**, *82*, 454. (k) Lo, K. K.-W.; Lau, J. S.-Y.; Fong, V. W.-Y.; Zhu, N. *Organometallics* **2004**, *23*, 1098. (l) Oshovsky, G. V.; Verboom, W.; Fokkens, R. H.; Reinhoudt, D. N. *Chem. Eur. J.* **2004**, *10*, 2739. (m) Seong, H. R.; Kim, D.-S.; Kim, S.-G.; Choi, H.-J.; Ahn, K. H. *Tetrahedron Lett.* **2004**, *45*, 723. (n) Kubo, Y.; Kato, M.; Misawa, Y.; Tokita, S. *Tetrahedron Lett.* **2004**, *45*, 3769. (o) Vazquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; Gonzales-Noya, A. M.; Bermejo, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1962. (p) Liu, S.-Y.; He, Y.-B.; Wu, J.-L.; Wei, L.-H.; Qin, H. J.; Meng, L.-Z.; Hu, L. *Org. Biomol. Chem.* **2004**, *2*, 1582. (r) Zlatuskova, P., Stibor, I.; Tkadlecova, M.; Lhotak, P. *Tetrahedron* **2004**, *60*, 11383. (s) Jose, D. A.; Kumar, D. K.; Ganguly, B.; Das, A. *Tetrahedron Lett.* **2005**, *46*, 5343. (t) Thiagarajan, V.; Ramamurthy, P.; Thirumalai, D.; Ramakrishnan, V. T. *Org. Lett.* **2005**, *7*, 657. (u) Gomez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *Org. Biomol. Chem.* **2005**, *3*, 1495.

(9) (a) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490. (b) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 520. (c) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 553. (d) Halgren, T. A.; Nachbar, R. B. *J. Comput. Chem.* **1996**, *17*, 587. (e) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 615. (f) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720. (g) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730.

(10) (a) Bryantsev, V. S.; Firman, T. K.; Hay, B. P. *J. Phys. Chem. A* **2005**, *109*, 832. (b) MMFF94 parameters reported in this reference for $N-C_a-N-H$ and $N-C_a-N-C$(alkyl) torsions are in error and have been corrected in Table 1.

(11) (a) Straatsma, T. P.; Aprà, E.; Windus, T. L.; Bylaska, E. J.; de Jong, W.; Hirata, S.; Valiev, M.; Hackler, M. T.; Pollack, L.; Harrison, R. J.; Dupuis, M.; Smith, D. M. A.; Nieplocha, J.; Tipparaju V.; Krishnan, M.; Auer, A. A.; Brown, E.; Cisneros, G.; Fann, G. I.; Fruchtl, H.; Garza, J.; Hirao, K.; Kendall, R.; Nichols, J.; Tsemekhman, K.; Wolinski, K.; Anchell, J.; Bernholdt, D.; Borowski, P.; Clark, T.; Clerc, D.; Dachsel, H.; Deegan, M.; Dyall, K.; Elwood, D.; Glendening, E.; Gutowski, M.; Hess, A.; Jaffe, J.; Johnson, B.; Ju, J.; Kobayashi, R.; Kutteh, R.; Lin, Z.; Littlefield, R.; Long, X.; Meng, B.; Nakajima, T.; Niu, S.; Rosing, M.; Sandrone, G.; Stave, M.; Taylor, H.; Thomas, G.; van Lenthe, J.; Wong, A.; Zhang, Z. *NWChem, A Computational Chemistry Package for Parallel Computers*, Version 4.6; Pacific Northwest National Laboratory: Richland, WA, 2004. (b) Kendall, R. A.; Aprà, E.; Bernholdt, D. E.; Bylaska, E. J.;

Dupuis, M.; Fann, G. I.; Harrison, R. J.; Ju, J.; Nichols, J. A.; Nieplocha, J.; Straatsma, T. P.; Windus, T. L.; Wong, A. T. *Comput. Phys. Commun.* **2000**, *128*, 260−283.

(12) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(13) (a) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007. (b) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.

(14) (a) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146. (b) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187. (c) Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, 31.

(15) *PCMODEL*; v. 9.2, 2006, Serena Software: Bloomington, IN.

(16) Ha, T.-K.; Puebla, C. *Chem. Phys.* **1994**, *181*, 47.

(17) Bencivenni, L.; Cesaro, S. N.; Pieretti, A. *Vib. Spectrosc.* **1998**, *18*, 91.

(18) Masunov, A.; Dannenberg, J. J. *J. Phys. Chem. B* **2000**, *104*, 806.

(19) Rostkowska, H.; Lapinski, L.; Khvorostov, A.; Nowak, M. J. *J. Phys. Chem. A* **2003**, *107*, 6373.

(20) Bharatam, P. V.; Moudgil, R.; Kaur, D. *J. Phys. Chem. A* **2003**, *107*, 1627.

(21) Lesarri, A.; Mata, S.; Blanco, S.; Lopez, J. C.; Alonso, J. L. *J. Chem. Phys.* **2004**, *120*, 6191.

(22) Patrito, E. M.; Cometto, F. P.; Paredes-Olivera, P. *J. Phys. Chem. B* **2004**, *108*, 15755.

(23) Vijay, A.; Sathyanarayana, D. N. *Spectrochim. Acta, Part A* **1993**, *49*, 1565.

(24) (a) Schrader, B.; Meier, W.; Gottlieb, K.; Agatha, H.; Barentzen, H.; Bleckmann, P. *Ber. Bunsen-Ges.* **1971**, *75*, 1263. (b) Bleckmann, P.; Schrader, B.; Meier, W.; Takahashi, H. *Ber. Bunsen-Ges.* **1971**, *75*, 1279.

(25) Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8891.

(26) Filleuxb, M. L.; Durandco, A. *Bull. Soc. Chim. Fr.* **1972**, 4710.

(27) (a) In contrast to many authors, we adopt standard organic nomenclature in accord with the Cahn−Ingold−Prelog system;[27b] that is, the cis form occurs when the two groups of highest priority are on the same side of a nonrotating bond. In this system, higher atomic number always has priority over lower atomic number. Since sulfur has a higher atomic number than nitrogen and since carbon has a higher atomic number than hydrogen, the cis isomer occurs when an attached carbon is on the sulfur side of the C_a-N bond and the trans isomer occurs when an attached carbon is on the nitrogen side of the C_a-N bond. (b) Robinson, M. J. T. In *Organic Stereochemistry*; Davies, S. G., Ed.; Oxford University Press: New York, 2000.

(28) Mido, Y.; Okada, H.; Fujita, N.; Kitagawa, I.; Kitahata, T.; Nashimoto, M.; Yoshida, H.; Matsuura, H. *J. Mol. Struct.* **1997**, *415*, 215.

(29) (a) Tompa, A. S.; Barefoot, R. D.; Price, E. *J. Phys. Chem.* **1969**, *73*, 435.

(30) (a) Price, E.; Sullivan, R. H. *Org. Magn. Reson.* **1975**, *7*, 142. (b) Martin, M. L.; Filleux-Blanchard, M. L.; Martin, G. J.; Webb, G. A. *Org. Magn. Reson.* **1980**, *13*, 396.

(31) Ramnathan, A.; Sivakumar, K.; Subramanian, K.; Janarthanan, N.; Ramadas, K.; Fun, H.-K. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1995**, *51*, 2446.

(32) Shen, Y.-H.; Xu, D.-J. *Acta Crystallogr.* **2004**, *E60*, 1193.

(33) Galabov, B.; Vassilev, G.; Neykova, N.; Galabov, A. *J. Mol. Struct.* **1978**, *44*, 15, and references therein.

(34) Custelcean, R.; Gorbunova, M. G.; Bonnesen, P. V. *Chem. Eur. J.* **2005**, *11*, 1459.

(35) Wozniak, K.; Wawer, I.; Strohl, D. *J. Phys. Chem.* **1995**, *99*, 8888.

(36) Hay, B. P.; Firman, T. K.; Moyer, B. A. *J. Am. Chem. Soc.* **2005**, *127*, 1810, and references therein.