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Methyl Rotational Barriers in Amides and Thioamides

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The methyl rotational barriers for a series of *N*-methyl-substituted amides and thioamides have been calculated at the MP2/6-311+G** level. A comparison of the *N*-methylformamide and methyl formate barriers indicates that the H−C(Me)−N−H eclipsed torsional arrangement destabilizes an amide by about 0.8 kcal/mol. A comparison of thioamides and amides showed the importance of steric repulsion between the sulfur and a methyl hydrogen in the *Z*-forms of the thioamides. The C−N bond rotation transition states of the *N*,*N*-dimethyl amides have much larger methyl rotational barriers than found in the ground states. They can be attributed to the smaller CH_{3}–N−CH_3 bond angles in the transition states.

Introduction

The conformations of peptides and proteins are in considerable part determined by the conformational preference for the amide group. As part of a general study of the properties of the amide group, we have examined the solvent dependence of the C−N rotational barrier for amides and thioamides both experimentally and theoretically.[1] The conformational preferences for the groups attached to the amide unit are also important, and as a part of the above investigations, we examined some of the methyl rotational barriers for *N*-methyl amides. There were interesting differences, and we have now carried out an extended study of these barriers and have attempted to determine the factors that control their magnitudes.

The compounds were studied via ab initio calculations at the MP2/6-311+G** theoretical level that has been found to reproduce experimentally determined barriers for other compounds[2] and includes diffuse functions that are thought to be important for properly representing lone pairs.[3] For the ground-state rotamers, geometry optimizations were initially carried out using C_s symmetry, followed by a calculation of the vibrational frequencies. If there were an imaginary frequency, this mode was examined and a group was rotated appropriately. Reoptimization, followed by a frequency calculation, led to rotamers with no imaginary frequencies. The data for these compounds are available as Supporting Information.

The methyl rotational transition states were also initially examined using C_s symmetry, and geometry optimization was followed by a frequency calculation. If just one imaginary frequency was found, and all of the convergence criteria had been met, the structure was accepted. If it were a second-order saddle point (i.e., two imaginary frequencies), these modes were examined, and a relaxed potential energy scan was carried out in which the torsional angle associated with the second imaginary frequency was varied stepwise while all other structural parameters were optimized. If a minimum were located, a transition state search was initiated using that structure, and its nature was examined via a calculation of the vibrational frequencies. In some cases, the scan did not lead to a structure with C_1 symmetry and only one imaginary frequency. When two methyl groups were rotated simultaneously, the resulting structure was expected to be a second-order saddle point.

Table S1 in the Supporting Information gives the conformations, symmetries, number of imaginary frequencies (in parentheses), the calculated total energies, and the dipole moments. It also gives the O═C−N−C torsional angles (τ_1), the O═C−C−H torsional angles (τ_2), and the C(═O)−N−C(Me)−H torsional angles (τ_3). The second of these applies only to the acetamides. For the thioamides, the corresponding torsional angles with S replacing O are given.

N-Methylformamide

A comparison of *N*-methylformamide and methyl formate provides a convenient starting point for an examination of methyl rotational barriers. The stationary points on the potential energy surface and their relative energies for methyl rotation are shown in Figure 1. The *Z*-conformers have the methyl group eclipsed with the carbonyl oxygen, and the second symbol refers to a methyl hydrogen being either syn (s) or anti (a) with respect to the carbonyl group.

With methyl formate, the *Z*-conformer has a lower energy than the *E*-form because of the energetically more favorable alignment of the C−O bond dipoles. Thus, the dipole moments of *Z* and *E* methyl formate are 1.99 and 4.92 D, respectively. The calculated difference in energy is 5.7 kcal/mol.[4] The same is true with *N*-methylformamide, except that the difference in energy is smaller (1.5

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[1] Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261. Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038.

[2] Karpfen, A.; Choi, C. H.; Kertesz, M. *J. Phys. Chem. A* **1997**, *101*, 7426.

[3] Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.

[4] Wiberg, K. B.; Bohn, R. K.; Jimenez-Vazquez, H. *J. Mol. Struct.* **1999**, *485*, 239. The experimentally determined energy difference is 4.8 ± 0.2 kcal/mol: Blom, C. E.; Günthard, Hs. H. *Chem. Phys. Lett.* **1981**, *84*, 267.

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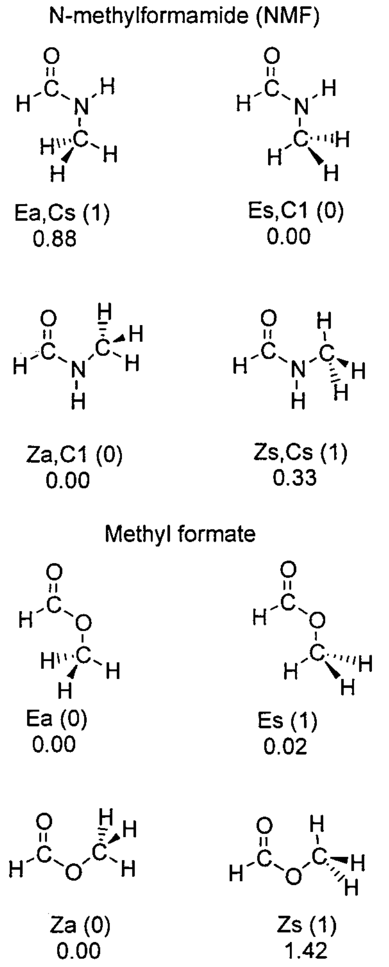

Figure 1. Rotamers of *N*-methylformamide and methyl formate.

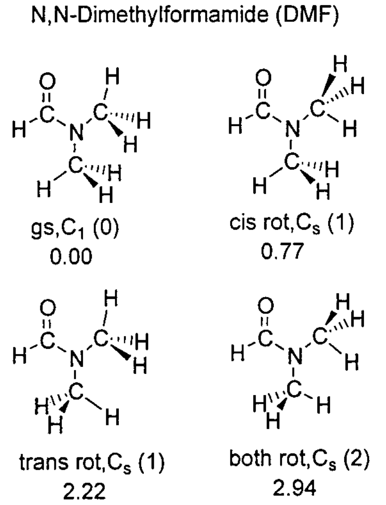

Figure 2. Rotamers of *N,N*-dimethylformamide.

kcal/mol) because the bond dipoles are smaller. Here, the dipole moments of *Z*- and *E*-*N*-methylformamide are 4.32 and 4.70 D, respectively. However, whereas *E*-methyl formate has a negligible methyl rotational barrier, *E*-*N*-methylformamide has a significant barrier. The reverse is true with the *Z*-forms. Here *Z*-methyl formate has a relatively large rotational barrier, whereas it is much smaller with *Z*-*N*-methylformamide.

The methyl formate barriers are easily understood. With the *Z*-form, there is a repulsive interaction between the carbonyl oxygen and an eclipsed methyl C−H bond which leads to the 1.4 kcal/mol calculated barrier (observed barrier is 1.2 kcal/mol[5]). The *E*-form does not have a repulsive interaction for the methyl group, and so it undergoes essentially free rotation. This assumption may be confirmed by the observation that when the formyl hydrogen is replaced by another group such as F or methyl, the methyl rotational barrier for the *E*-forms becomes relatively large.[4]

The lowest energy conformer for the amide is *Za*, and surprisingly it has a pyramidal nitrogen ($\alpha = 16°$). The H−N−C(Me)−H torsional angle is 24°. This suggests that this torsional angle is destabilizing when it is 0°. Such an assumption will account for the difference between the esters and amides. It would be responsible for the 0.88 kcal/mol barrier for the *E*-amide and for the reduction in the *Z*-amide barrier from 1 kcal/mol in the ester to 0.3 kcal/mol in the amide. It should be noted that the C_s structure for *Za* is only 0.04 kcal/mol higher in energy than the C_1 form. This indicates that the molecule is quite "floppy".

It might also be noted that the O···H repulsive interaction in the amide leads the C−N−C bond angle to go from 120.7° in *Za* to 123.0° in *Zs*.

N,N-Dimethylformamide

The rotational barriers for the two methyl groups are significantly different (Figure 2). The ground state (GS) adopts a slightly distorted C_1 structure, but the C_s form is only 0.03 kcal/mol higher in energy. It has an O···H repulsive interaction, and when the methyl cis to the carbonyl group is rotated, the energy increases by 0.8 kcal/mol.[6] Here the O···H repulsion ($\sim$1.4 kcal/mol as in methyl formate) in the GS is replaced by a *cis*-Me−N−C−H torsional interaction in the cis-rotated form suggesting that the latter leads to a 2.2 kcal/mol net destabilization. The repulsive interactions can be seen in the bond angles: $\angle$(O)C−N−Me(cis) = 120.6° in the GS and 118.0° in the cis-rotated form; $\angle$Me−N−Me = 117.6° in the GS and 119.8° in the cis-rotated form.

The energy of the form with a rotated trans methyl group is still higher because it has both repulsive interactions and its energy relative to the GS (2.2 kcal/mol) is in accord with the above estimate of the *cis*-Me−N−C−H interaction. When both methyl groups are rotated, the relative energy increases to 2.9 kcal/mol, the sum of the two independent methyl rotational barriers. This shows that the rotation of the two methyl groups is relatively independent.

The methyl rotational barriers for the C−N bond rotational transition states also were examined and were found to be considerably larger than those for the ground state. In TS1, the barrier is calculated to be 3.82 kcal/mol, and in TS2, it is 3.43 kcal/mol. One major difference between the ground state and the transition states is found in the Me−N−Me bond angles. In the ground state

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(5) Demaison, J.; Boucher, D.; Dubrulle, B. P.; van Eijck, B. P. *J. Mol. Spectrosc.* **1983**, *102*, 260. Plummer, G. M.; Herbst, E.; DeLucia, F.; Blake, G. A. *Astrophys. J. Suppl. Ser.* **1986**, *60*, 949.

(6) The torsional barriers in this report appear to be derived mainly from steric interactions. This is not always the case, and with ethane other factors are responsible for the barrier (Pophristic, V.; Goodman, L. *Nature* **2001**, *411*, 565).

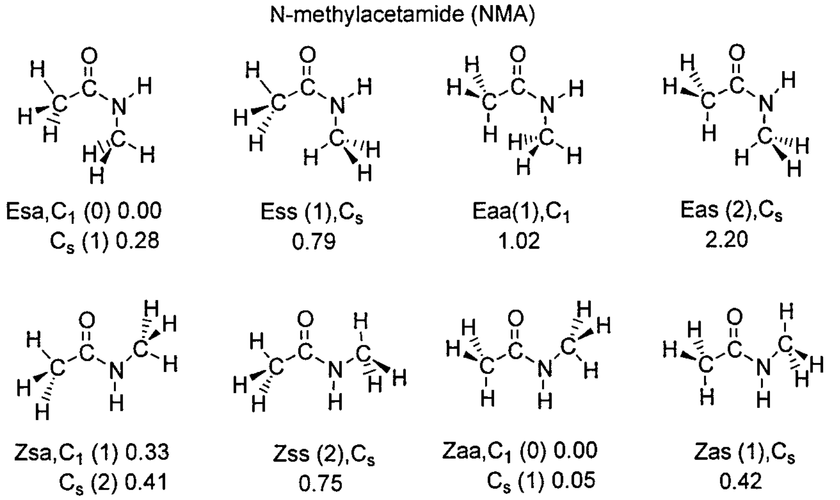

Figure 3. Rotamers of *N*-methylacetamide.

the angle is 117.6°, and the smaller transition state angles (110.5°) bring the methyl groups together, increasing the barrier.

This is similar to the observations of Pophristic and Goodman[7] concerning dimethyl ether. The methyl rotational barrier in the ether is 4.8 kcal/mol but decreases to 3.6 kcal/mol when the ether is protonated. Here the Me−O−Me bond angle is increased by protonation, leading to a smaller interaction between the methyl groups and a smaller barrier.

N-Methylacetamide

Here, there are two rotational barriers, for the *C*-methyl and *N*-methyl groups. With acetamide (AA) itself, the lowest energy structure has a C_1 structure with the O═C−C−H torsional angle = 23.8°,[8] and the C_s structure is higher in energy by 0.4 kcal/mol. The *C*-methyl rotational barrier is only 0.08 kcal/mol. This may be compared with the barrier in *Z*-methyl acetate, 0.25 kcal/mol. The reduced barrier in the ester and amide as compared to aldehydes and ketones (1.2 kcal/mol in acetaldehyde,[9] methyl hydrogen eclipsed with carbonyl) is probably due to the reduced positive charge of the carbonyl carbon that results from donation of the O or N lone pair electrons to the electron deficient carbon.

The lowest energy *E*- and *Z*-*N*-methylacetamide conformers also have C_1 structures with the C_s structure about 0.3 kcal/mol higher in energy in the *E* conformer but with little energy difference for the Z conformer.

With the *Z* forms, the *C*-methyl group has a weak preference to be staggered with respect to the carbonyl group (Figure 3). The energy of the *Zsa* conformer is 0.4 kcal/mol greater than that for *Zss*, which is essentially the same as found for the *Za* and *Zs* conformers of NMF. The difference in relative energy of *Zaa* and *Zas* is also essentially the same. Thus, the *C*-methyl group has no significant effect on the barrier when the *N*-methyl group is directed away from the *C*-methyl group.

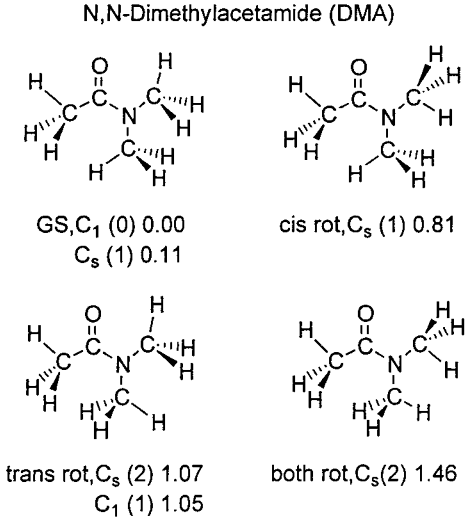

Figure 4. Rotamers of *N*,*N*-dimethylacetamide.

With the *E*-forms, the *C*-methyl group prefers to be eclipsed with the carbonyl group, probably to minimize the repulsive interaction between the *C*- and *N*-methyl groups. The relative energies of *Esa* and *Ess* are reversed with respect to *Ea* and *Es* of NMF. The Me···Me repulsive interaction is the dominant factor with the *E*-forms and can be seen in the bond angles. In the series with increasing relative energies, *Esa*, *Ess*, *Eaa*, and *Eas* the Me−C−N bond angles are 115.8, 116.9, 117.4, and 119.3°, respectively, and the C−N−C angles are 126.4, 128.5, 127.8, and 131.0°, respectively. They may be compared with the corresponding angles in the low-energy *Zaa* conformer, Me−C−N = 115.8° and C−N−C = 122.6.° It might also be noted that the difference in energy between the most stable *E* and *Z* forms of NMA is 2.3 kcal/mol, significantly greater than for NMF (1.5 kcal/mol).

N,*N*-Dimethylacetamide

The ground-state rotamer of *N*,*N*-dimethylacetamide (Figure 4) is considerably distorted from planarity (Table 1). A H of the *C*-methyl group has a 3.5° torsional angle with the carbonyl group. The cis *N*-methyl group has a 9.0° O═C−N−C torsional angle and a −36.8° C−N−C−H torsional angle, and the trans *N*-methyl group has a

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[7] Pophristic, V.; Goodman, L. *J. Phys. Chem. A* **2000**, *104*, 3231.

[8] Jeffrey, G. A.; Ruble, J. R.; McMullan, R. K.; DeFrees, D. J.; Pople, J. A. *Acta Crystallogr.* **1980**, *B36*, 2292. Wong, M. W.; Wiberg, K. B. *J. Phys. Chem.* **1992**, *96*, 668.

[9] Kilb, R. W.; Linn, C. C.; Wilson, E. B., Jr. *J. Chem. Phys.* **1957**, *26*, 1695. Iijima, T.; Kimura, M. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2159.

162.2° O=C–N–C torsional angle and a 40.4° C–N–C–H torsional angle. When the structure is made planar, the energy rises by 0.11 kcal/mol.

The transition state in which the *N*-methyl cis to the carbonyl group is rotated ~60° has a 0.81 kcal/mol higher energy, which is similar to the corresponding DMF conformers. However, the form having the rotated group trans has a 1.07 kcal/mol higher energy, which is much lower than for the corresponding DMF rotamer. When both methyl groups are rotated, the energy increases to 1.46 kcal/mol.

These relative energies may be rationalized if one assumes that the C–Me···N–Me interaction in the ground-state and cis-rotated forms destabilizes them by ~1.2 kcal/mol, the syn Me–N–C–H interaction in all of the rotated forms destabilizes them by 2.2 kcal/mol, and the O···H nonbonded interaction in the ground-state and trans-rotated forms destabilizes them by 1.4 kcal/mol. The latter values are in accord with the interactions in the molecules described above.

The transition states for C–N bond rotation again have higher barriers. The TS1 methyl rotational barrier is 3.97 kcal/mol, and the TS2 barrier is 4.52 kcal/mol. These barriers are somewhat larger than those for NMA.

N-Methylthioformamide

The thioamides are of some interest in that they have larger C–N rotational barriers than amides and also a stiffer NR_2 out-of-plane wagging potential.[10] In the *E*-form, the methyl rotational barrier is somewhat reduced as compared to *N*-methylformamide (Figure 5). The more interesting change is the increase in the barrier for the *Z*-form, which is over 1 kcal/mol greater than that for the corresponding formamide. In esters, and presumably also amides, there is a repulsive interaction between the oxygen and a methyl group attached to O or N. Sulfur is much larger than oxygen, and so it is not surprising that the repulsive interaction between sulfur and an eclipsed hydrogen of a methyl group would be still larger.

The conclusion concerning the sulfur nonbonded interactions can be confirmed by examining the methyl thioformate rotamers (Figure 5). The rotational barrier for the *E*-forms remains small, but that for the *Z*-forms increases from 1.42 kcal/mol for methyl formate to 2.51 kcal/mol in methyl thioformate.

The difference in repulsive interactions in the thioamides can be seen in the C–N–C bond angles. For NMF, the angles are the following: *Za*, 120.7°; *Zs*, 123.0°. For the thioamide they are the following: *Za*, 122.4°; *Zs*, 125.0°.

N,*N*-Dimethylthioformamide

In the lowest energy conformer of *N*,*N*-dimethylformamide, the *Z*-methyl group is rotated so that a methyl hydrogen is eclipsed with the carbonyl oxygen (Figure 2). Here, the *cis*-Me–C–N–H torsional interaction is greater than the O···H nonbonded interaction. However, with the thioformamides (Figure 6), the *Z*-methyl group is rotated so that it is not eclipsed with the sulfur. Again, this must result from the larger size of the sulfur, making the S···H nonbonded interaction the dominant term.

N-Methylthioacetamide

A comparison of *N*-methylacetamide (Figure 3) with *N*-methylthioacetamide (Figure 7) is interesting. The *E*-forms have close to the same relative energies as for NMA showing that the replacement of oxygen by sulfur has little effect on the barrier as long as the *N*-methyl group is not close to the sulfur. However, there are marked changes in the relative energies of the *Z*-forms, with the rotamers having a methyl hydrogen eclipsed with the sulfur having an increase in energy of about 1.5

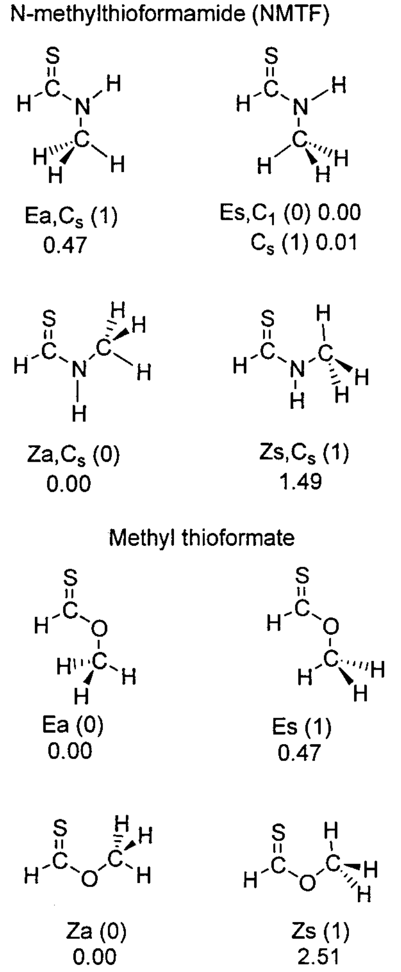

Figure 5. Rotamers of *N*-methylthioformamide and methyl thioformate.

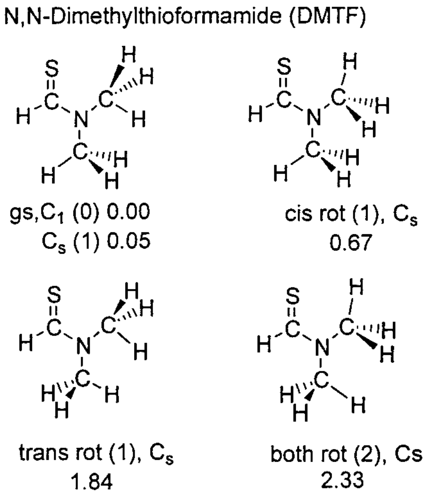

Figure 6. Rotamers of *N*,*N*-dimethylthioformamide.

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[10] Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201.

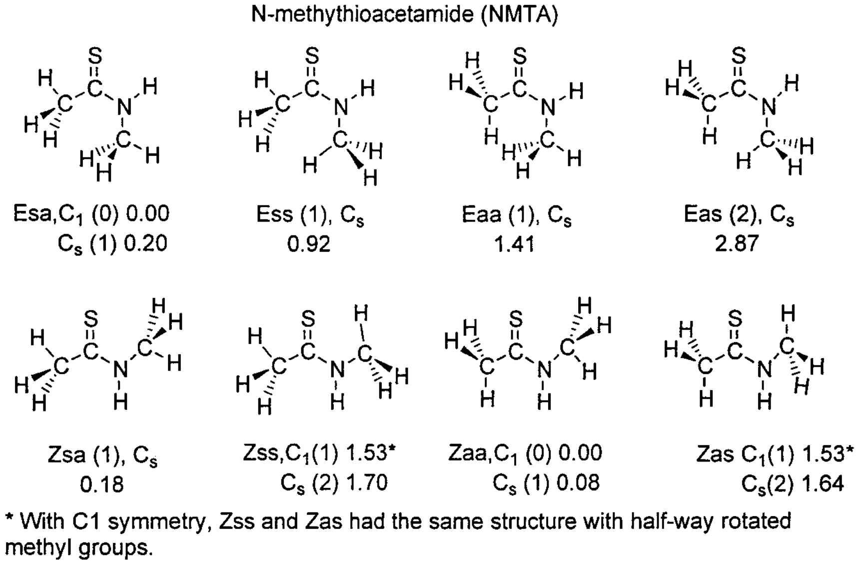

Figure 7. Rotamers of *N*-methylthioacetamide.

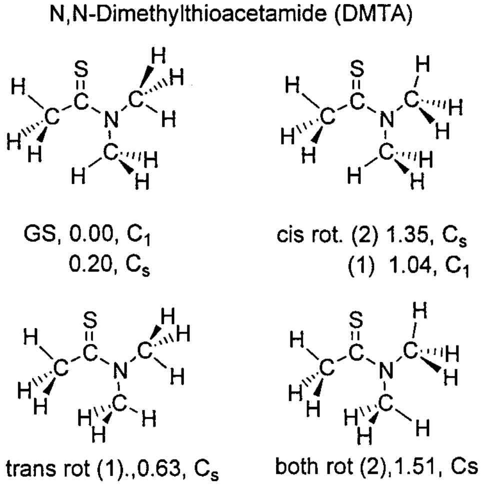

Figure 8. Rotamers of *N*,*N*-dimethylthioacetamide.

kcal/mol. This again shows the importance of the S···H nonbonded repulsion.

N,*N*-Dimethylthioacetamide

The ground-state rotamer of *N*,*N*-dimethylthioacetamide (Figure 8) has a rotated *Z*-methyl group as compared to the ground-state rotamer of dimethylacetamide (Figure 4). This is the same as was seen with the corresponding formamides and leads to significant differences in relative energies of all of the dimethylthioacetamide rotamers as compared to the dimethylacetamides.

Conclusions

The methyl rotational barrier for the formamides results from a combination of O···H nonbonded repulsions and H−C−N−H or Me−C−N−H torsional interactions (maximum energy at 0°) with the latter being the larger interaction. In the acetamides, there is an additional repulsive interaction between an *N*-methyl hydrogen and the acetyl methyl group.

The thioamides have similar interactions, but here the S···H nonbonded repulsion is larger than the H−C−N−H torsional interaction. As a result, for *N*,*N*-dimethylthioacetamide, the relative energies of the ground-state and cis-rotated forms are reversed from those of *N*,*N*-dimethylacetamide. Another difference between the amides and thioamides is that C_1 structures with partially rotated acetyl methyl groups and somewhat pyramidalized amide nitrogens are common with the former but are infrequently found with the latter. This is probably another manifestation of the relatively stiff out-of-plane deformation modes for the thioamides.

Calculations

The ab initio calculations were carried out using Gaussian-99.[11] In each case, the species was characterized as a minimum energy, transition state or second-order saddle point by a calculation of the vibrational frequencies at the MP2/6-311+G** level.

Acknowledgment. This investigation was supported by a grant from the National Institutes of Health.

Supporting Information Available: A table of the calculated energies, dipole moments, key torsional angles, and relative energies for all of the amide rotamers and calculated atomic coordinates of the minimum energy amide rotamers. This material is available free of charge via the Internet at http://pubs.acs.org.

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