Hindered Rotation in Thioureas: Steric Effects and **Conformations**^{†§}

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Abstract-The temperature dependent spectra of several mono-, di- and trialkylthioureas have been recorded. Free energy barriers to internal rotation about the C-N bonds have been calculated. In thioureas that were unsymmetrically substituted, free energy barriers were found to be different for each C—N bond with the more substituted amino group exhibiting the higher barrier. The monosubstituted thioureas showed different rotational barriers for the NH2 groups of the cis and trans isomers, respectively. The free energy barriers for the trans isomers were found to be substituent dependent and substantiate the reassignment of the high and low field substituent signals to the trans and cis isomers, respectively. The spectrum of 1-methyl-3-t-butylthiourea indicates restricted rotation of the t-butyl group at temperatures below 200 K.

INTRODUCTION

RECENT studies of substituted thioureas have shown that these molecules possess appreciable double bond character in the C-N bond due to electron delocalization across the C-N bond. A previous NMR study of 1-methylthiourea,¹ in which only two isomers are possible, allowed speculation about the assignment of the methyl resonances in the cis and trans isomers, but did not provide conclusive evidence to support the assignments. Prior to this paper, other workers^{2,3} published results which indicated that the assignment of NMR resonances in the spectrum of 1-methylthiourea should be reversed from previous assignments. The two isomers are



in which the corrected assignment attributes the high field signal to the trans-methyl protons of I(a) and the low field signal to the cis-methyl protons of I(b). A pronounced solvent dependence of the isomer ratio in 1-methylthiourea has also been reported.^{1,2} Walter and Reuss² presented evidence for hydrogen bonding and proposed a cyclic dimer as the hydrogen bonded species. These authors demonstrated how strong hydrogen bond acceptors could break up the intermolecular hydrogen bond in the cyclic dimer and cause the *cis* form to become the predominant isomer.

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Walter and Reuss⁴ have also reported results of an NMR study of 1,3-dialkylthioureas which have three possible isomers, for example, 1,3-dimethylthiourea



These investigators found two unequal doublets for II at -50 °C in CD₃CN. The ratio of intensity of these doublets was 3:2, and was attributed to isomers II(a) and II(b). However, no assignment was made as to which doublet represented forms II(a) and II(b). Moreover, there seems to have been some doubt in excluding form II(c), because high concentration and polar solvents favor the trans conformation.² In this paper, results are reported in pyridine- d_5 and support the existence of only forms II(a) and II(b).

During the course of this work an interest developed in the effect of steric factors in determining conformations and barriers to rotation about the C--N bond. In order to add to the total picture of the behavior of the thioureas, a comparative study of rotational barriers about the different C--N bonds within the same molecule in unsymmetrically substituted thioureas was performed by analyzing the total NMR spectrum. This paper also presents a study of simple mono-, di- and trialkyl substituted thioureas in order to confirm signal assignments and to further understand steric effects in these compounds.



(1) $R_1 = R_2 = R_3 = R_4 = H$ (5) $R_1 = R_3 = CH_3$; $R_2 = CH_3$ $R_4 = H$ (2) $R_1 = CH_3$; $R_2 = R_3 =$ (6) $R_1 = R_3 = CH_3CH_2$; $R_2 =$ $R_4 = H$

EXPERIMENTAL

Source of compounds

1-Methylthiourea (2), 1,3-di-isopropylthiourea (7), 1,3-di-*t*butylthiourea (8), 1,1,3-trimethylthiourea (11) and tetramethylthiourea (12) were obtained from Aldrich Chemical Company; 1-ethylthiourea (3) was obtained from K & K laboratories; thiourea (1) was obtained from J. T. Baker Chemical Company; 1,1dimethylthiourea (9) was a gift from Dr James Oliver, U.S. Department of Agriculture, Beltsville Md; 1-*t*-butylthiourea (4) and 1-*t*-butyl-3-methylthiourea (10) were prepared in our laboratory; *t*-butyl isothiocyanate and methylamine hydrochloride were obtained from Diaprep Incorporated.

Thioureas 4 and 10 were prepared according to the method of Schmidt, Striewsky, Seefelder and Hitzler.⁵ The reaction consisted simply in bringing the *t*-butyl isothiocyanate into contact with the corresponding amine. Thiourea 4 was recrystallized twice from boiling methanol-water and dried *in vacuo*; m.p. 171 to 172 °C. Thiourea 10 was prepared according to the authors⁵ but was used without further treatment; m.p. 107 to 109 °C. Before use compounds 2, 11 and 12 were each recrystallized from ethanol-ethyl acetate. The melting points were 119 to 120 °C, 83 to 84 °C and 76 to 77 °C, respectively. 1,3-Dimethylthiourea was recrystallized from thanol-ligroin; m.p. 64 to 65 °C. High purity 1,3-diethyl thiourea (6) and 1,3-di-*t*-butylthiourea (8) were ordered from the manufacturer, but upon receipt the compound 6 was slightly yellow and 8 was brownish. Each compound was dissolved in chloroform, the resulting solutions filtered to remove insoluble matter and the solvent removed *in vacuo* to yield the white solid in each case; the thiourea 6, m.p. 77 to 78 °; the thiourea 8 sublimed at 159 °C. Compounds 1, 3, 7 and 9 were obtained in very high purity and were used without further treatment.

The preparation of the deuterated compounds was performed as follows. The undeuterated compound was dissolved in D_2O and allowed to equilibrate for several hours followed by removal of the solvent *in vacua*. This procedure was repeated twice to insure complete deuteration (>99.5%). The proton NMR spectra of the compounds showed no residual spin-spin coupled signal but did show a small isotopic shift (0.2 Hz) of the methyl proton resonances of the deuterated compounds to higher field than the mean frequency of the corresponding spin-spin doublets in the undeuterated compounds.

Preparation of solutions

Solutions were prepared by weighing directly into the NMR tube the appropriate amount of compound and adding solvent to a predetermined fiducial mark to give the desired concentrations (0.5 or 1.0 M). Solutions whose spectra were to be analysed by the total lineshape method (TLS) were degassed using the freezepump-thaw technique and sealed under vacuum with the solution at liquid nitrogen temperatures. In other cases, solutions were not degassed and were closed with a regular NMR cap. In acetone- d_6 solutions of undeuterated compounds, it was important to keep the samples at very low temperatures until just prior to running the spectra and to perform the temperature dependent studies by working upward. This precaution was necessary to avoid spectral changes due to proton exchange between the *enol* form of acetone- d_6 and the amino protons of the thiourea in solution.

Spectral conditions

The spectra were recorded on a Varian A-60 NMR spectrometer equipped with the variable temperature accessory mentioned below. The field was optimized just prior to recording each spectrum. The chemical shifts were measured by calibrating the chart paper at the sweep width to be used by generating side bands with a Hewlett and Packard model 200CD wide range oscillator whose frequency of oscillation was monitored with a Hewlett-Packard model 521C electronic counter. In cases where the lines whose chemical shift was to be measured were sharp enough (in the slow exchange region), their separation was measured by adjusting the audio oscillator until their respective first order sidebands simultaneously superimposed the parent signals, and recording the observed frequency of the oscillator. When running spectra, a suitable reference line, such as one of the residual pyridine lines in pyridine- d_5 solutions, was chosen approximately 500 Hz downfield from internal TMS. The chemical shift of the chosen line was measured by the technique of superimposition of the TMS sideband and was used to calibrate the chart paper for that particular spectrum assuming linearity. The assumption of linearity was confirmed within 1 Hz by a spot check of some of the other shifts in the same spectrum by the superimposition technique.

The Varian V-6040 variable temperature accessory was used to control the temperature. The Varian reference samples of methanol and ethylene glycol were calibrated using a Leeds-Northrup potentiometer equipped with a copper-constantan thermocouple. The temperature was monitored by the substitution method using either the calibrated methanol or ethylene glycol reference samples.

Decoupling experiments were performed using the Varian model V-6058A spin decoupler.

RESULTS AND DISCUSSION

Spectra, Signal Assignments and Conformations

The CH₃ region of the spectrum of 1,3-dimethylthiourea (5) in pyridine- d_5 at room temperature appears as a sharp doublet (J = 4.7 Hz) due to spin-spin coupling with the N-H protons. As the temperature is lowered the doublet broadens until it appears as a single broad resonance which separates at even lower temperatures into an unequal pair of chemically shifted doublets. At temperatures between 225 and 214 K, evidence of a third resonance is also seen. For 1,3dimethylthiourea- d_2 in pyridine- d_5 , the CH₃ protons appear as a singlet at room temperature. The singlet broadens and eventually separates into two unequal singlets as the temperature is lowered (Fig. 1). At 214 K a shoulder (C) appears on one of the main peaks (A). The separation between A and C is 2.5 Hz while the separation between A and B is 25.7 Hz. In acetone- d_6 solution, 1,3-dimethylthiourea- d_2 gives three distinct



FIG. 1. NMR spectrum of the methyl protons of deuterated (ND) 1,3-dimethylthiourea- d_2 (1 M) in pyridine- d_5 at 60 MHz and a sweep width of 500 Hz.



FIG. 2. NMR spectra of the methyl protons in (a) undeuterated (NH) 1,3-dimethylthiourea (1 M), (b) deuterated (ND) 1,3-dimethylthiourea- d_2 (1 M) in acetone- d_6 at 60 MHz and a sweep width of 50 Hz.

lines, and 1,3-dimethylthiourea gives six distinct lines due to spin-spin coupling with N—H protons (Fig. 2). A seventh line (D) which appears in the spectrum of 1,3-dimethylthiourea (5) is due to the presence of a small amount of the deuterated form of the compound as a result of proton exchange with the *enol* form of acetone d_6 . The separation between lines A and B of 1,3dimethylthiourea- d_2 in acetone- d_6 is 11 Hz, less than half the separation of the same lines in pyridine- d_5 (Table 1). The separation between lines A and C in acetone- d_6 is 2.5 Hz, which is the same as that for A—C in pyridine d_5 . Apparently, the A–B separation is solvent dependent, while the A–C separation is not affected by solvent in these instances. Line A is assigned to the *cis* CH₃

Table 1. Temperature dependence of the chemical shift difference between the NMR signals of the methyl protons of isomers of 1,3-dimethylthiourea- d_2

	In acet	one- d_6^a	In pyridine- d_5^a		
Т	$(v_{\rm A} - v_{\rm B})$	$(v_{\rm A} - v_{\rm C})$	$(v_{\rm A} - v_{\rm B})^{\gamma}$	$(\nu_{\rm A} - \nu_{\rm C})$	
(K)	(Hz)	(Hz)	(Hz)	(Hz)	
257			b		
253	b		_		
252			16.8		
249	7.8	_			
246	_		21.3		
244	10.0	_			
241			23.2		
238	10.5	—	_		
236	10.8		24.6		
233	10.8	b			
230			25.2		
228	10.9			—	
225	10.9	2.1	25.5	2.5	
220	11.1	2.3	26.1	2.5	
214	11.1	2.5	25.7	2.5	
210	10.9	2.5	_		
205	11-1	2.6		—	

^a Concentration 1 M. See Figs. 1 and 2 for identification of NMR signals. Precision of chemical shifts ± 0.2 Hz. ^b Coalescence temperature. protons of structure II(b) and line B is assigned to the trans CH₃ protons. The third line C is assigned to the cis-cis CH_3 protons of structure II(a). There is no obvious reason to expect, a priori, that the cis CH_3 of forms II(a) and II(b) should be in very different magnetic environments. In any case their magnetic environments should be more similar to each other than to the environment of the trans CH₃. The area ratio for resonances A, B and C are 2:2:1, respectively. If structures II(a) and II(b) were of equal concentration, the cis-methyl resonance of II(a) would be twice that of each resonance representing the cis- and transmethyls in II(b). If the assignment is correct, the concentration of II(b) is four times that of II(a). Isomer II(c) may be ruled out as one of the contributing forms in the NMR spectrum on the basis of steric and electrostatic grounds. On the basis of solely electrostatic effects, II(c) would be the most favored in a polar solvent. Space-filling models indicate that steric interaction involving methyl groups precludes assumption of a planar structure which would allow efficient porbital overlap between carbon and nitrogen in the trans-trans isomer. The spectra support the conclusion that none of the trans-trans isomer is present, since this would tend to alter the isomer ratios and possibly produce a fourth line in the spectrum of 1,3-dimethylthiourea- d_2 .

Figure 3 describes the spectrum of 1-t-butylthiourea (4) over a large temperature range. Similar spectra were obtained for 1-methyl-(2) and 1-ethyl-(3) thioureas, respectively. Chemical shifts of these compounds in pyridine- d_5 at low temperatures are listed in Table 2. The spectrum (Fig. 3) of 1-t-butylthiourea shows two unequal resonances (A and B) in the CH₃ region at



FIG. 3. NMR spectra of 1-t-butylthiourea (0.5 M) in pyridine d_5 at 60 MHz and a sweep width of 1000 Hz.

Table 2. Chemical shift data of monosubstituted thiourea isomers in pyridine- d_5 at 60 MHz



^a Relative to internal TMS.

^b Concentration equals 1.0 M except for 1-t-butylthiourea (0.5 M).

^e The methyl resonance is a triplet with $J(CH_2, CH_3) = 7.2$ Hz.

^d Resonances 5 and 6 are triplets with $J(H(5), CH_2(A)) = 5.5$ Hz.

^e Resonances 5 and 6 are quartets with $J(H(5), CH_3(A)) = 4.5$ Hz and $J(H(6), CH_3(B)) = 4.7$ Hz.

temperatures between 244 and 210 K. The resonances (A and B) coalesce at 248 K and become a sharp singlet at 291 K. In the NH, NH₂ region at 215 K, the spectrum comprises six resonance lines. Resonance line 4 appears as a shoulder on line 6, but is definite as deduced from area ratio measurements. As the temperature is increased lines 3 and 4 coalesce into a single line at 227 K; lines 5 and 6 coalesce at 247 K; lines 1 and 2 at 251 K.

The spectrum of 1-methylthiourea (2) in pyridine- d_5 may be described as follows. Two unequal spin-spin doublets (J = 4.5 and 4.8 Hz) appear in the CH₃ region at 277 K. At higher temperatures these lines coalesce into a single broadened resonance and at approximately 38 °C appear as a sharp spin-spin doublet (J = 4.6 Hz). In the NH, NH₂ region at 215 K, the spectrum comprises six lines, as in the case of 1-t-butylthiourea. As the temperature is increased, singlets 3 and 4 coalesce into a single line 7 at 223 K; singlets 1 and 2 coalesce next at 273 K; multiplets 5 and 6 coalesce at 294 K. Lines 5 and 6 are quartets where line 6 partially overlaps with line 2. The following equilibria apply to the assignment of lines in the spectra of 1-alkylthioureas.



Lines 5 and 6 were assigned to the *trans* and *cis* NH positions, respectively, by decoupling experiments and

peak area comparisons in the spectrum of 1-ethylthiourea (3). The triplet of line 5 became a singlet while simultaneously irradiating the frequency of the low field CH_2 protons (A); likewise, line 6 became a sharp singlet while simultaneously irradiating the high field CH_2 protons (B). The peak area ratios of lines



FIG. 4. Representative NMR spectra of symmetrically substituted dialkylthioureas in pyridine- d_5 at 60 MHz and a sweep width of 1000 Hz. (a) 1,3-dimethylthiourea (1 M); (b) 1,3-diethylthiourea (1 M); (c) 1,3-di-isopropylthiourea (0.5 M); (d) 1,3-di-t-butylthiourea (0.25 M); (e) 1-t-butyl-3-methylthiourea (1 M)at 209 K; (f) 1-t-butyl-3-methylthiourea (1 M) at 197 K.

6:5, (1 + 2): (3 + 4) and B:A were equal to 2:1 within experimental error at 215 K.

It is apparent from the analysis of the spectra at various temperatures that 1-alkylthioureas are characterized by three different barriers to internal rotation, and that the barriers for the NH_2 protons of the *cis*and *trans*-alkyl isomers are different. The difference in the rotation of the NH_2 group in these isomers allows them to be analyzed as individual two-site exchange processes.

Representative spectra of 1,3-disubstituted thioureas are shown in Fig. 4. Single resonances are shown for both the *t*-butyl and NH proton lines in the spectrum (Fig. 4d) of 1,3-di-*t*-butylthiourea (8). In the spectrum (Fig. 4e) of 1-methyl-3-*t*-butylthiourea (10), evidence for only the *cis-trans* isomers is shown by the presence of only two signals for the CH₃ protons (A and B), two signals for the *t*-butyl protons (C and D), and the four corresponding signals in the NH region (A', B', C' and D', respectively). The chemical shifts are listed in Table 3. The spectrum may be explained in terms of the equilibrium in Eqn (5).



Lines A and B are assigned to the *cis*- and *trans*-methyl protons, respectively, and lines C and D to the cis- and trans-t-butyl protons, respectively, as indicated in Eqn (5). At lower temperatures (e.g. Fig. 4f), the t-butyl peak broadens and additional peaks begin to appear. These peaks may be due to sterically induced restricted rotation of the t-butyl group, that is, the methyl groups begin to occupy magnetically distinct positions. The corresponding NH peak, D', has separated into two peaks of apparently equal area, D_1' and D_2' . The appearance of the NH lines provides evidence of the disposition of the t-butyl group. Spacefilling molecular models show that a rotation of the NH proton out of the molecular plane is necessary in order to facilitate rotation of the *t*-butyl group which occupies the *trans* position in the thiourea molecule. It is therefore conceivable that as the *t*-butyl rotation becomes slower in the NMR time domain, the partial rotation of the t-butylamino group out of the molecular plane creates a magnetic environment for NH protons which is distinct from the inplane environment. Of course, the NH proton can be out of the plane in an up or down manner, both of which would be magnetically equivalent. One can visualize a kinetic process wherein the NH protons occupy one of three possible sites, two out-of-plane and one planar. It is obvious that partial rotation of the NH proton into either the up or down nonplanar position from the planar position is equally probable. If partial rotation is allowed only between adjacent

TABLE 3. CHEMICAL SHIFT DATA OF 1,3-DIALKYLTHIOUREAS IN PYRIDINE- d_5 at 60 MHz

	Т			$\Delta^{\mathbf{b}}$		
Compound	(K)	R	NMR line ^a	(Hz)	Kc	%cis-trans Isomer
(5) CH ₂	215	CH ₃	В	181.2	4.38	81
(0) 0113		5	A + C	206.0		
		NH	A' + C'	529.5		
			B'	588.2		
(6) CH ₃ CH ₂	215	CH2	В	204.5	2.65	73
		-	A + C	243.1		
		CH ₃		73.6e		
				82·5e		
		NH	A' + C'	526-1		
			B	575.3		
(7) (CH ₂) ₂ CH	224	CH	В	257·0	0.63	39
		CH_3		75.5		
		NH	A' + C'	486.3		
			B′	548·0		
(8) (CH ₃) ₃ C	215	t-Bu		100.3		
() ())		NH		469.6		
(10) $(CH_3)_3C_3$	209	t-Bu	D	96.1	6.33 ^d	86 % D
CH ₃			С	107.9		
2		CH ₃	В	176-5	6·42 ^d	86 % A
		-	Α	198.8		
		NH	A'	481·2		
			B'	575.5		
			C'	412.5		
			D'	517·0		
	197	NH	A'	486.4		
			B'	584.6		
			C'	419·2		
			D_1'	550.9		
			D.'	506.9		

* See Fig. 4 and structure IV; all lines labeled in an analogous manner.

^b Relative to TMS.

^d K = D/C or A/B.

e Overlapping triplets.

^e Equilibrium between *cis-trans* and *cis-cis* form, K = (A + B)/C, where C = (A + C) - B. NMR line C represents *cis-cis* form.

sites, that is, only between planar and nonplanar and never directly between the two nonplanar sites, and neither the planar nor nonplanar is energetically favored, the equality of the NMR signals may be explained. Under the above conditions, the kinetic process is a simple exchange between two equally probable sites. The lower field signals in all thioureas mentioned thus far have been assigned to the cis protons. On the basis of these earlier assignments and the assumed chemical shift anisotropy of the C=S bond, D1' is assigned to the in-plane and D_2' to the near planar NH protons.

Free Energy Barriers

Calculation of free energy barriers entailed an experimental determination of the pseudo first order rate constant (k) using the lineshape equations of Gutowsky and Holm.⁶ This rate constant, or its reciprocal $(k^{-1} = \tau)$ was substituted into the appropriately modified Eyring equation⁷ to calculate the free energy of activation. The details involved in such calculations have been presented elsewhere8,9 and are not repeated here. Several authors have demonstrated the extent of errors usually present in activation parameters determined by NMR techniques.¹⁰⁻¹² Therefore, and also due to the comparative nature of this work, only the most reliable quantity, $\Delta G^{\ddagger}_{\ddagger}$ is reported. $\Delta G^{\ddagger}_{\ddagger}$ was determined by the following methods: total lineshape (TLS), coalescence, peak separation and peak intensity ratio. In some cases, it became impractical to determine ΔG [‡] by the TLS method. However, for some compounds, ΔG^{\dagger} was calculated by the three methods and the values obtained agreed within one percent or better.

A comparison of the rotational barriers for monoalkylthioureas listed in Table 4 establishes the validity of comparison between barriers calculated from NH and $N\dot{H}_2$ proton signals, and those calculated from substituent (R) proton signals. The barriers to rotation about the same C-N bond calculated from the different spectral lines are equal within experimental error.

TABLE 4. FREE ENERGY BARRIERS TO INTERNAL ROTATION IN MONO-ALKYLTHIOUREAS IN PYRIDINE- d_5 BY COALESCENCE METHOD

Compounda	Т _с ь (К)	C—N bond	NMR signals ^e	Δv_o^d (Hz)	ΔG^{+e}_{+} (Kcal/mol)
(2) CH ₃	294	$C_2 - N_1$	5 & 6 (NH)	36.5	14.7
., .	286	$C_2 - N_1$	A & B (R)	15.5	14.7
	273	$C_2 - N_3$	1 & 2 (NH ₂)	53.9	13.3
	223	$C_2 - N_3$	3 & 4 (NH ₂)	55.6	10.8
$(3) CH_3CH_2$	283	$C_{2} - N_{1}$	A & B	25.6	14.3
	282	$C_2 - N_1$	5&6	33.3	14.1
	270	$C_2 - N_3$	1 & 2	54.6	13.2
	230	$C_2 - N_3$	3&4	58.2	11.2
(4) (CH ₃) ₃ C	248	$C_2 - N_1$	A & B	12.3	12.8
	247	$C_2 - N_1$	5&6	12.9	12.7
	251	$C_2 - N_3$	1 & 2	102.9	11.9
	228	$C_2 - N_3$	3 & 4	83.6	10.9

^a Concentrations are 1 M for compounds 2 and 3 and 0.5 M for 4. (1 to 4).

^d Extrapolated non-exchanging chemical shift.

^e No significant temperature dependence was found beyond the mit of experimental error which was ± 0.1 kcal/mol.

Substituent Effects on the Barriers to Internal Rotation

Table 5 summarizes the effect of increasing the substituent size and the number of alkyl groups substituted on the nitrogen atoms. In the monoalkyl substituted thioureas, there are three energy barriers given for the following: (1) rotation about the $C_2 - N_1$ bond which was determined from the alkyl proton signals and independently from the NH proton signals, (2) rotation about the C_2 — N_3 bond in the *trans* isomer and (3) rotation about the C_2 -N₃ bond in the cis isomer. The latter two rotational barriers were determined from the time-dependence of the NH₂ proton

TABLE 5. FREE ENERGY BARRIERS OF ALKYL SUBSTITUTED THIOUREAS IN PYRIDINE- d_5

Compound	$\Delta G^{+a,t}_{+a,t}$ (kcal/mol	$\Delta G^{t,t}_{t,t}$ (kcal/mol)
(1) Thiourea	13.7	13.7
(2) 1-Methylthiourea	14.7	13.3,° 10.8 ^d
(3) 1-Ethylthiourea	14.3	13.2,° 11.2ª
(4) 1-tert-Butylthiourea	12.8	11.9,° 10.9d
(9) 1.1-Dimethylthiourea	12.6	12.0
(5) 1.3-Dimethylthiourea	12.7	12.7
(6) 1.3-Diethylthiourea	11.7	11.7
(7) 1.3-iso-Propylthiourea	11.5	11.5
(8) 1.3-Di-tert-butylthiourea	e	e
(0) 1-tert-Butyl-3-methylthiourea	11.7	11.7
(1) 1.1.3-Trimethylthiourea	10.7	e
12) 1,1,3,3-Tetramethylthiourea	е	e

^a Rotational barrier about the C₂-N₁ bond, calculated from the alkyl group resonance signal.

^b Rotational barrier about the C₂-N₃ bond, calculated from the NH resonance signal.

^c Rotational barrier about the C_2 — N_3 bond in the *trans* isomer. ^d Rotational barrier about the C_2 — N_3 bond in the *cis* isomer.

^e Singlet at all observed temperatures in pyridine-d₅.

^f ΔG_{\pm}^{\pm} is constant over the temperature range studied to within ± 0.1 kcal/mol.

resonance shape as a function of temperature. The rotations about the C-N bonds are indicated in Eqns (1 to 4). There is an apparent decrease in the rotational barriers about the C2-N1 bond and the C_2 -N₃ bond of the *trans* isomer in the series methyl (2), ethyl (3) and t-butyl (4) compounds. However, rotational barriers about the C_2 - \hat{N}_3 bond in the cis isomers of these compounds seem to be independent of these substitutents.

The rotational barriers about the $C_2 - N_1$ bond in 1-methyl- and 1-ethyl-thioureas are higher than in thiourea, but in *t*-butylthiourea the barrier is lower. There are three factors that may play an important role in the explanation of these results; namely, (1) increased electron delocalization across the C-N bond, (2) steric interaction between the N-alkyl groups and the NH protons that are trans to the thiocarbonyl sulfur, and (3) stabilization of the ground state by intermolecular hydrogen bonding.

Substitution of an alkyl group on nitrogen increases the electron density around nitrogen by the inductive effect; therefore, more electrons will be available for delocalization across the double bond. Increased electron delocalization will add more double bond character to the C-N bond, thereby raising the barrier to rotation about the C-N bond. On the other hand, steric interactions between the *N*-alkyl group and the proton (NH_2 group) in the *trans* positions may produce bond distortions such that the C_1NCSNC_3 atoms are not exactly planar and thereby cause a decrease in the extent of electron delocalization across the C—N bond. The barrier to rotation about the C—N bond will therefore decrease if the alkyl group becomes too bulky as in the case of the *t*-butylthiourea (**4**).

The energy barrier to rotation about the C_2 —N₃ bond in the *trans* isomers of the methyl (2) and ethyl (3) compounds is approximately equal to that of thiourea, which is 1.8 Kcal less in the *trans-t*-butylthiourea. The rotational energy barrier about the C_2 —N₃ bond in the *cis* isomers of compounds 2, 3 and 4 are lower than in thiourea, but are independent of the substituted alkyl group. This seems reasonable since the steric interaction between the protons of the NH₂ group and the R substituent of the NHR group will be less in the *cis* than in the *trans* isomers.

In the disubstituted compounds a similar trend of decreasing barriers to internal rotation with increasing substitutent size is observed. The observed barriers are progressively less for 1,3-dimethyl-(5), 1,3-diethyl-(6) and 1,3-di-isopropyl-(7) thiourea, respectively, in pyridine- d_5 solution. The spectrum of 1,3-di-t-butylthiourea (8) was a singlet at all observed temperatures in pyridine d_5 , but exhibited a barrier of 11.6 Kcal/mol in CDCl₃ solution. Isaksson and Sandström¹³ observed free energy barriers that were an average of approximately 1.1 Kcal/mol higher for thiourea in CDCl_a than for the same compounds in pyridine for a large number of compounds. If the above value for 1,3-di-t-butylthiourea (8) in pyridine- d_5 is corrected accordingly, a barrier of 10.5 Kcal/mol in CDCl₃ is obtained. Generally, the barriers are lower for disubstituted thioureas than for monosubstituted thioureas containing the same alkyl group. Apparently, the introduction of a second substituent into the molecule increases steric repulsion between the substituents, which forces the $C_1 NCSNC_3$ skeleton to deviate more from planarity than in the case of monosubstituted thioureas.

A comparison of 1,1-dimethyl-(9), 1,1,3-trimethyl-(11) and 1,1,3,3-tetramethyl-(12) thiourea manifests the same trend. A decrease of approximately 2 Kcal/mol is observed in going from compound 9 to 11 which contains an additional methyl group. As in the monosubstituted thioureas, the unsymmetrically substituted thioureas (9 and 11) show different energy barriers about the C_2 - N_1 and C_2 - N_3 bonds. In compound 9, the energy barrier for the C_2 — N_1 bond is slightly higher than for the C_2 — N_3 bond, 12.6 and 12.0 Kcal/mol, respectively. However, in compound 11, the energy barrier to rotation about the $C_2 - N_1$ bond is considerably greater than about the C2-N3 bond. The barrier for the C_2 — N_1 bond is 10.7 Kcal/mol and the barrier for the C_2 -N₃ bond is undetermined due to the existence of a single signal at temperatures as low as -120 °C in CDCl₃. It can be inferred therefore, that the 3-methylamino group in 11 is still rotating rapidly on the NMR time scale at the lowest observed temperatures in pyridine d_5 (Fig. 5). Complete substitution of methyl groups for hydrogens on the nitrogens produces a nonplanar configuration and apparently no delocalization of electrons on nitrogen can occur; hence, there is very little or no double bond character in the C-N bonds.



FIG. 5. The 60 MHz spectra of the methyl protons of (a) and (b) undeuterated, and (c) deuterated (NH) 1,1,3-trimethyl-thiourea in acetone- d_6 .

Only a single proton resonance line has been observed for 1,1,3,3-tetramethylthiourea at temperatures as low as -120 °C.¹⁴

Table 6 summarizes isomer ratios (K = trans/cis) for methyl-, ethyl- and t-butyl-thiourea in pyridine- d_5 . The ratios obtained from the alkyl resonance of the spectrum are more accurate than those obtained from the amino proton resonances because of some overlap of these lines. The isomer ratio of 1-methylthiourea agrees with the value obtained in previous work¹ to within 5%. An increase in the amount of trans isomer is observed in going from 1-t-butyl- or 1-ethylthiourea to 1-methyl-thiourea. These results also indicate that steric interactions involving substituents in the trans position are very important. Similar results are also observed in the 1,3-dialkyl substituted thioureas (Table 3).

Table 6. Equilibrium constants for *cis* to *trans* interconversion of *N*-alkylthiourea in pyridine- d_5

	T	K		
Compound	(K)	(<i>Irans/cis</i>)		
		CH ₃ protons-	Annie protons	
(2) CH ₂	215	2.26	2.2	
(-) - 5	220	2.12	2.2	
	231	1.82	2.0	
	243	1.57	1.8	
	248	1.48		
	258	1.33		
	273	1.15		
	278	1.10		
		CH ₂ protons ^b		
(3) CH ₂ CH ₂	215	1.92	2.2	
() 2	220	1.81	2.0	
	231	1.58	1.6	
	241	1.42		
	243	1.39		
	248	1.33		
	258	1.19		
	278	1.01		
		<i>t</i> -Bu protons ^e		
(4) $(CH_3)_3C$	215	2.02	2.0	
	227	1.70	2.0	
	238	1.48	2.1	
	241	1.43	2.1	
	244	1.37	1.9	

a $\log K = -1.04 + (299/T).$ c lo

 $b \log K = -0.956 + (267/T).$

Comparison with Other Work

Isaksson and Sandström¹³ have reported results of a systematic study of the effect of changing the conjugative capacity at one of the nitrogen atoms in several 1,1dimethyl-3-phenylthioureas; likewise, evidence of a conjugative effect upon the barrier was also apparent in the results of Brown and Katekar.¹⁴ These investigations¹³ were designed to show the importance of the phenyl group in affecting the barrier by introducing electron-donating and electron-attracting groups into the para position of the ring. The free energy barriers which were reported ranged from 11.4 Kcal/mol for 1,1-dimethyl-3-p-nitrophenylthiourea to 10.5 Kcal/mol for 1,1-dimethylthiourea. This change is certainly in the expected direction, but in the intervening compounds the reported differences did not exceed the range of normal experimental error for this type of investigation. The authors¹³ stated that 1,1,3-trimethylthiourea (11) was chosen as the reference compound because it has no extra conjugation and negligible steric effects. The present work indicates that considerable steric interactions are present in the compound. Indications are that the 3-methylamino group is characterized by a much lower barrier to internal rotation than the 1,1dimethylamino group, due primarily to steric effects. In acetone- d_6 (Fig. 5) at 38 °C 1,1,3-trimethylthiourea (11) shows a singlet for the 1,1-dimethylamino group and the 3-methylamino group appears as a doublet due to coupling with the NH group (J = 4.2 Hz). The singlet and doublet were observed in the ratio of 2:1. The 1,1-dimethylamino signal broadens at lower temperatures and splits into a doublet at -60° ($\Delta v_0 =$ 17.4 Hz). The upfield doublet remained sharp even at -75 °C. The conclusion is that thiourea 11 is not a suitable reference compound for the purpose of investigating conjugative effects.

Attempts to measure rotational barriers in tetramethylthiourea (12) and tetramethylselenourea¹⁶ by the NMR techniques have failed since the compounds give singlets in their respective spectra down to -120 °C. This is a further manifestation of a steric effect, but Sandström¹⁵ suggests that the low barriers must partly be due to the strong electron-donating effect of the dimethylamino group. Here it is not clear what the author means since in 1,1-dimethylthiourea the barrier to internal rotation is slightly higher for the dimethylamino group than for the NH₂ group in the same molecule (9).

The general trend observed in studies of amide-like molecules was an increase in rotational barriers upon going from amides to thioamides to selenoamides. The results of Neumann and Jonas¹⁷ gave a difference of 4.9 Kcal/mol between N,N-dimethylacetamide- d_3 and N,N-dimethylthioacetamide- d_s . Jensen and Sandström reported a difference of about 1 Kcal/mol between thioamides and selenoamides, and stated that the difference between the thioamides and selenoamides was probably diminished by a small steric effect in the selenoamides due to the larger van der Waals radius of 2.0 Å for selenium compared to 1.85 Å for sulfur.¹⁶

A similar trend has been observed in the urea, thiourea and selenourea compounds. The only reported NMR study of the free energy barrier in urea18 gives a value of 11.3 Kcal/mol; in thiourea, ΔG^{\ddagger} is 13.7 Kcal/mol as determined in the present

In 1,1-dimethylthiourea (9), ΔG ; is 12.6 work. Kcal/mol for the dimethylamino rotation as compared to 14.6 Kcal/mol for the rotation about the corresponding bond in 1,1-dimethylselenourea.¹⁹ After comparing $\Delta G^{\ddagger}_{\ddagger}$ of 14.6 Kcal/mol in 1,1-dimethylselenourea with the value of 14.0 Kcal/mol for 1-methylthiourea reported earlier,¹ Reeves, Shaddick and Shaw¹⁹ suggested that a downward adjustment of the reported $\Delta G^{\dagger}_{\star}$ in 1-methylthiourea would be expected upon re-examination of the spectral data for the compound. The present work indicates that no downward adjustment is in order and that any comparison of barriers between other than structurally analogous ureas, thioureas and selenoureas is not entirely valid due primarily to steric effects. For example, 1,1dimethylurea must be compared with 1,1-dimethylthiourea and 1,1-dimethylselenourea.

Infrared studies by Gosavi, Agarwala and Rao²⁰ on several alkylthioureas provided evidence of possible association through hydrogen bonds. The authors assigned spectral bands to cis, trans and bonded NH. Lane et al.²¹ reported similar IR bands for 1-methylthiourea, but did not make assignments. For 1,3di-t-butylthiourea (8), equal cis and trans NH bands were observed in the IR spectrum, but three resonances were observed in the *t*-butyl region of the NMR spectrum and were attributed to the presence of three different rotamers.20 The present work shows no indication of different rotamers in the NMR spectrum of the thiourea 8 (Fig. 4d) which consists of two lines in the ratio of 9:1 in pyridine- d_5 .

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