# Application of <sup>15</sup>N Spectroscopy and Dynamic NMR to the Study of Ureas, Thioureas and their Lewis Acid Adducts

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Rotational barriers and <sup>15</sup>N chemical shifts have been measured in a number of ureas and thioureas. As anticipated on the basis of the <sup>15</sup>N shifts, several previously unobserved rotational barriers could be detected by using lanthanide reagents or a high field spectrometer. Nearly constant effects on both the rotational activation energy and the <sup>15</sup>N shift are produced on going from ureas to the corresponding thioureas, and correlations are found between the  $\Delta G^{\ddagger}$  and  $\delta^{15}$ N values. The results are discussed in terms of lone pair delocalization, and anomalies with respect to the general behaviour are tentatively explained in the light of the effect of steric torsion in crowded structures on the <sup>15</sup>N shifts and rotation barriers.

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# **INTRODUCTION**

Many investigations, especially in the field of dynamic NMR, have been devoted to the structure of ureas and thioureas but conflicting interpretations have often been proposed.<sup>1-23</sup> Measurement of the rotational barriers around the C-N bond is capable of yielding useful information about the electronic and steric factors which control the ground state configuration. Unfortunately, relatively few activation parameters have been determined in ureas, and the failure to observe decoalescence phenomena at low temperatures has been frequently ascribed to a value for the barrier below the range usually accessible by NMR ( $\Delta G_{T}^{\dagger} <$  $25 \text{ kJ mol}^{-1}$ ). Although this behaviour seems reasonable in crowded molecules such as  $(CH_3)_2NCON(CH_3)_2$ (1) or  $(CH_3)_2NCON(CH_2CH_3)_2$  (2),<sup>1-4</sup> where steric strain can lead to distorted structures, it is more surprising in compounds such as  $(CH_3)_2NCONH_2$  (3)  $(CH_3CH_2)_2NCONH_2$  (4)<sup>5</sup> or RHNCONHR' (R, R' =  $CH_3$ ,  $C_2H_5$ ) where steric strain is certainly much less noticeable.

More results have been obtained concerning thioureas, and this situation has generally been attributed to the fact that rotational barriers in the



Here again steric repulsion between the nitrogen substituents *trans* to the sulphur atom are considered to be responsible for a very low barrier in tetramethylthiourea and for the absence of a conformation of type C in N,N'-disubstituted thioureas  $\begin{array}{cccc} H & & R & & H \\ R-N & H-N & R & & R-N \\ H-N & H-N & R & R-N \\ A & B & C \end{array}$ 

In fact, the roles and the relative importance of electronic and steric factors in ureas and thioureas are not always clear. Thus, when a complex is formed between the oxygen atom of **5**, CH<sub>3</sub>NHCONHCH<sub>3</sub>, and a Lewis acid such as BF<sub>3</sub>, a conformation of type C becomes significantly populated.<sup>5</sup> In this respect an X-ray study has shown that, in spite of a marked torsion of the skeleton, two methyl groups are allowed to occupy simultaneously a position *trans* to the carbonyl group in crowded ureas.<sup>6</sup> As much less steric hindrance is expected between N—H and N—CH<sub>3</sub> or N—CH<sub>2</sub>CH<sub>3</sub> groups it seems likely that the lack of observable splittings at low temperatures is not always the result of a very low barrier and the hypothesis of fortuitous signal equivalence cannot be systematically disregarded.

From another point of view, when interpreting the trends of rotational barriers in terms of structural features, the question is always raised of eventual variations in the transition state which could obscure the behaviour of the ground state. It is therefore especially helpful to dispose of another parameter which could be related to the electronic structure of the ground state. We have shown that good correlations between the nitrogen chemical shift and the rotational barriers can be found in several series of conjugated compounds.<sup>23-26</sup> As the <sup>15</sup>N chemical shift directly reflects properties of the ground state, and of

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some excited states, it can be used to detect possible anomalies associated with effects specific to the rotational transition state. Conversely, detailed examination of such relationships can be of assistance for a better understanding of the relative importance of the various factors which govern nitrogen chemical shifts.

# EXPERIMENTAL SECTION

#### Samples

Most of the ureas and thioureas are commercial products and were purchased from Aldrich or Fluka. Compounds 9 and 10 were synthesized from the reaction of N,N-dimethylcarbamoyl chloride with the corresponding amine, and 11, 12 and 31 result from the reaction of phosgene with the primary amines. The complexes which are formed between ureas (or thioureas) and Lewis acids were prepared as described elsewhere.<sup>26</sup> Owing to low solubility, sensitivity limitations were often encountered in natural abundance <sup>15</sup>N NMR, especially at 6.08 MHz. Therefore, most of the samples were dissolved in water-ethanol mixtures (saturated solutions).

#### NMR

<sup>15</sup>N spectra were recorded on a Brüker WP 60 spectrometer (SW = 6000 Hz. PW<sub> $\pi/2$ </sub> = 11.10<sup>-6</sup> s. Resolution 0.3 ppm) or on a Brüker WH90 DS spectrometer (SW = 6000 Hz. PW<sub> $\pi/2$ </sub> = 27.10<sup>-6</sup> s. Resolution 0.15 ppm). 2000–50 000 scans were accumulated depending on the nature of the nitrogen atom

 $(-NH_2, NH \text{ or } N-)$ . To overcome sensitivity limi-

tations, due to unfavourable  $T_1$  values, the relaxation reagent Cr(acac)<sub>3</sub>was added (0.08 M) to the N,Ndisubstituted derivatives. An acidic (2 M NO<sub>3</sub>H)D<sub>2</sub>O solution of 30% <sup>15</sup>N enriched sodium nitrate (4 M), contained in a 3 mm o.d. capillary provided both the nitrogen reference and the lock substance. This capillary tube was centred in the 15 mm o.d. sample tubes. The NO<sub>3</sub><sup>-15</sup>N signal is at -2.6 ppm (low frequency) from external CH<sub>3</sub>NO<sub>2</sub>.

The <sup>1</sup>H and <sup>13</sup>C spectra were obtained with a Varian XL-100-12 spectrometer [SW = 5000 Hz. PW<sub> $\pi/2$ </sub> (<sup>13</sup>C) = 28.10<sup>-6</sup> s. Resolution = 0.05 ppm] and a Cameca 250 superconducting apparatus operating in the CW(<sup>1</sup>H) or FT(<sup>13</sup>C) mode [SW = 12 500 Hz. PW<sub> $\pi/2$ </sub>(<sup>13</sup>C) = 10.10<sup>-6</sup> s. Resolution 0.02 ppm]. The number of scans was 200–1000 at room temperature, and 1000–10 000 at low temperatures. The temperatures were controlled and measured using the device already described.<sup>44</sup> For the simple coupled, or decoupled, two site exchanges the kinetic parameters were determined by a total lineshape analysis using the RMNTAU program.<sup>12</sup> For the more complex systems exhibited by **7** and **24**, for example, a multisite exchange program adapted from Ref. 40 was

utilized. The chemical shift differences at the considered temperature, T, were estimated by measuring the chemical shift difference at several temperatures in the slow exchange domain and extrapolating the results to temperature T. The free energy of activation  $\Delta G_T^{\dagger}$  was computed according to the Eyring equation:

 $\Delta G_{\rm T}^{\ \ \sharp}(\rm kJ\ mol^{-1}) = 8.31\ T(23.77 + \ln\ T/\rm k + \ln\ \kappa)$ 

# RESULTS

#### Rotational barriers about C-N bonds

Values of free energies of activation for the rotation around the C—N bond of ureas and thioureas are collected in Tables 1 and 2. As these parameters are lower than in amides, the coalescence phenomena are usually less easily obtained. Moreover, as far as the rotation of the NH<sub>2</sub> groups is concerned, difficulties arise from signal broadening due to the quadrupolar relaxation of <sup>14</sup>N. Thus, a number of previous experiments have failed to provide quantitative results.

With a view to bringing the coalescence temperature into a higher, and thus more easily accessible, range or to eliminate accidental degeneracy of the signals we performed low temperature experiments in the presence of the shift reagent Eu(fod)<sub>3</sub>.<sup>27,28</sup> In the <sup>13</sup>C spectrum a splitting of the methyl signals of 3, (CH<sub>3</sub>)<sub>2</sub>NCONH<sub>2</sub>, is effectively observed at approximately 230 K for a concentration ratio of the lanthanide complex and the substrate,  $\rho$ , of about 0.8. Similarly, two carbon signals are separated at approximately 230 K in a solution of tetramethylurea containing Eu(fod)<sub>3</sub> in a concentration ratio  $\rho \approx 1$ . A broadening of the carbon signals of 6 [(CH<sub>3</sub>CH<sub>2</sub>)<sub>2</sub>N]<sub>2</sub>CO was also obtained at 200 K for a concentration ratio  $\rho \simeq 0.2$  but no splitting occurred at temperatures down to 190 K for the tetramethylthiourea  $\rho \simeq 0.5$ . In the hypothesis of a first order exchange process these coalescence figures would correspond to  $\Delta G^{\dagger}$  values of approximately 52 kJ mol<sup>-1</sup> for **3**,  $43 \text{ kJ mol}^{-1}$  for **1** and  $41 \text{ kJ mol}^{-1}$  for **6**. Owing to the drastic sensitivity limitations which arise in <sup>13</sup>C investigations of coalescence patterns at low temperatures, a detailed study of the lineshape behaviour as a function of the concentration of the lanthanide complex was not performed, and the values given above must be considered as approximate. Moreover, caution should be exercised in interpreting the results. When lowering the temperature of solutions containing lanthanide shift reagents the possibility occurs that intermolecular exchange processes are sufficiently slowed down for the free and complexed substrate molecules to be observed separately. It should be noted, nevertheless, that such phenomena have usually been detected<sup>29</sup> at temperatures lower than those mentioned above and for solutions containing a large excess of substrate. Therefore, the observed lineshape variations are probably attributable to the hindered rotation process around the C--N bond. In fact, as a

Observed	×	No	s <sup>15</sup> N/NO -	Solvent	s <sup>13</sup> C_O	AC <sup>‡</sup> (T)	Column 1	
HanCOX	NH.	8	- 302 4	H_O/EtOH	161 9	47 2 (220)		nei. Q
12000	diprotonated species	Ŭ	- 243 8ª	'manic acid'	101.5	47.2 (220)	'magic acid'	26
	NHCH	7	- 304 8 <sup>i</sup>	H <sub>a</sub> O/FtOH	162 6-161 99	$\simeq 41 (220)^{1}$		
	N(CH <sub>a</sub> ) <sub>a</sub>	3	- 303 6	H <sub>2</sub> O/EtOH	168.0 <sup>h</sup>	40 9(211)		_
	$N(CH_2CH_3)_2$	4	- 304.2	H <sub>2</sub> O/EtOH	157.5°	39.7 (205)	$(CD_3)_2CO$	_
(CH <sub>a</sub> ) <sub>2</sub> NCOX	NH2	3	- 306.4		168.0°	44.5 (211)	(CD <sub>2</sub> ) <sub>2</sub> CO	
3.22	+ BF <sub>2</sub>					65.2(276)		5
	NHCH <sub>2</sub>	9	315.7 <sup>i</sup>	H <sub>2</sub> O/EtOH	159.6	{ 29.2 <sup>d</sup>	2 2 3 - 2	14
	3			2		<37	(CD <sub>2</sub> ) <sub>2</sub> CO	_
	+ SbCl <sub>5</sub>					59.3 (273)°	CH <sub>2</sub> Cl <sub>2</sub>	11
	N(CH <sub>3</sub> ) <sub>2</sub>	1	- 315.3	Neat	165.5	26.3 (135)	CHFCl <sub>2</sub> /(CD <sub>2</sub> ) <sub>2</sub> CO	37-41
	+ SbCl <sub>5</sub>		- 304.8			50.1 (226)	CH <sub>2</sub> Cl <sub>2</sub>	11
	diprotonated species		<b>232.8</b> <sup>b</sup>	'magic acid'	151.1	>83 (>373)	'magic acid'	36
	NH[CH(CH <sub>3</sub> ) <sub>2</sub> ]	10	-310.0	H <sub>2</sub> O/EtOH	156.8	40.5 (298)	CHFCl <sub>2</sub> -3-fluoro-	10
	+ SbCl <sub>s</sub>					54,7 (298)	CD <sub>2</sub> Cl <sub>2</sub>	38
	N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub>	2	-314.9	CDCl <sub>2</sub>	163.4 <sup>h</sup>	<33	CD <sub>2</sub> Ċl <sub>2</sub>	_
	+ TiCl <sub>4</sub>		290	CD₂Cl₂	149.9	53.1		
CH <u>₃N</u> HCOX	NH <sub>2</sub>	7	- <b>306</b> <sup>i</sup>	H₂O/EtOH	162.6–161.9 <sup>9</sup>	55.2 (253) <sup>f</sup>	СН₃ОН	
	NHCH <sub>3</sub>	5	- 310.2	EtOH	161.0	k		
	+ BF <sub>3</sub>					66.9 (288)	CH <sub>2</sub> Cl <sub>2</sub> /CH <sub>3</sub> NO <sub>2</sub>	5
	$NH(CH_2CH_3) + SbCl_5$	11				66.9 (288)	CH <sub>2</sub> Cl <sub>2</sub> /CH <sub>3</sub> NO <sub>2</sub> (CD <sub>3</sub> ) <sub>3</sub> CO	11
	N(CH <sub>3</sub> ) <sub>2</sub>	9	<b>309.8</b> <sup>i</sup>	H <sub>2</sub> O/EtOH	159.6	(<37) <sup>i</sup>	3.2	_
CH₃CH₂ <u>N</u> HCOX	NHCH <sub>3</sub> +SbCl <sub>5</sub> NHCH <sub>2</sub> CH <sub>3</sub>	11 12	- 291.3	H <sub>2</sub> O/EtOH		66.9 (293)	CH <sub>2</sub> Cl <sub>2</sub>	11
	+BF <sub>3</sub>			~		65.2(287)	$CH_2CI_2/CH_3NO_2$	5
(CH_)_CHNHCOX	NHCH(CH_).	31	– <b>277</b> 0	H <sub>2</sub> O/EtOH	157.3	k		_
(013)2011111007	$N(CH_3)_2$	32	-275.7	H <sub>2</sub> O/EtOH	156.8	k		
(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> NCOX	NH <sub>2</sub>	4	- 281.3	H₂O/EtOH	157.5	43 (205)	(CD <sub>3</sub> )₂CO	
	+ BF3	~	000 0		a co. ab	65.6 (287)		5
		2	- 289.9		163.4"	< 33.4		
		~	-2/5		149.9	50.1 (253)		
	$N(CH_2CH_3)_2$	D	~ 288.4	iveat	0.001	< 33.4		

 Table 1. Parameters of ureas and some complexes of ureas with Lewis acids. The carbonyl chemical shift is referred to TMS.

 The free energy of activation is given in kJ mol<sup>-1</sup> and the temperature in Kelvin. Most of the <sup>13</sup>C spectra are obtained in CDCl<sub>3</sub>

<sup>a</sup> Estimated from results of Ref. 36. <sup>b</sup>  $\delta$ NH(CH<sub>3</sub>)<sub>2</sub><sup>+</sup> = 317.6 ppm. <sup>c</sup> In methanol. <sup>d</sup> Slow rotation of the (CH<sub>3</sub>)<sub>2</sub>N group in trimethylurea has been observed below 178 K by proton NMR.<sup>11</sup> The value given is for  $E_a$ ,  $T_c = 203$  K.<sup>14</sup> <sup>e</sup> Attributed to a ligand exchange process between urea and the SbCl<sub>5</sub>-urea adduct.<sup>11 f</sup> From **7A** (CH<sub>3</sub> *cis* to CO) to **7B** (CH<sub>3</sub> *trans* to CO).  $\Delta G_{B\rightarrow A}^{\pm} = 51.4$  kJ mol<sup>-1</sup>. <sup>a</sup> In a mixture of methanol and acetone at 223 K. 161.9 ppm is for the more abundant isomer **7A**. <sup>h</sup> Neat. <sup>i</sup> The assignment of the nitrogen atoms has been confirmed by recording the coupled spectrum: <sup>1</sup>J(NH) = 91.3 Hz in 9 <sup>1</sup>J(N,H-2) = 87.9 and <sup>1</sup>J(NH) = 91.6 in 7. <sup>i</sup> The isomer with CH<sub>3</sub> *cis* to CO is probably largely predominant or exclusively present. <sup>k</sup> One isomer is probably largely predominant. <sup>i</sup> As the exchange phenomena involve the overlapping signals of two conformational isomers, the lifetime determinations are not very accurate.  $\Delta G^{+} \approx 41$  kJ mol<sup>-1</sup> in **7A**;  $\Delta G^{+} \approx 42$  kJ mol<sup>-1</sup> in **7B**.

large proportion of the substrate is involved in a complex with the lanthanide derivative, a substantial enhancement of the activation energy is expected. In this respect the rotational barrier in the dimethyl carbamate-Eu(fod)<sub>3</sub> adduct, for example, is shown to be considerably higher than in the free substrate.<sup>28</sup>

Although no splitting is observed in the 60 MHz proton spectra of **3** and **4** in  $CH_2Cl_2$  or acetone solutions down to 193 K,<sup>5</sup> we have succeeded in observing decoalescence of the proton lines at 250 MHz in  $(CD_3)_2CO$  (Table 1). Thus, at 211 K the methyl signal of **3** begins to split into two components separated by 0.09 ppm. The decoalescence of the NH<sub>2</sub> signal also occurs at 211 K but the chemical shift

difference now reaches 0.24 ppm. For **4** the two methyl multiplets are separated ( $\Delta \delta = 0.085$  ppm) at 205 K and the NH<sub>2</sub> signal splits into two components ( $\Delta \delta = 0.56$  ppm) at about the same temperature.

In a solution containing approximately 2 moles of the urea 2 and  $1\pm0.05$  mole of TiCl<sub>4</sub>, the <sup>1</sup>H NMR spectra of the free and complexed species are separated at about 230 K. By further lowering the temperature a splitting ( $\approx 0.4$  ppm) of the *N*-methyl resonance assigned to the complexed urea is obtained at about 253 K at 250 MHz. This results from a hindered rotation around the C—N(CH<sub>3</sub>)<sub>2</sub> bond of the adduct, corresponding to a free energy of activation of about 50 kJ mol<sup>-1</sup>.

Observed								
nitrogen atom	x	No	δ <sup>15</sup> N/NO <sub>3*</sub>	Solvent	δ <sup>13</sup> C==S	ΔG <sup>‡</sup> <sub>exp</sub> (T)	Solvent	Ref.
H₂ <u>N</u> CSX	NH <sub>2</sub>	13	-270.7	H <sub>2</sub> O/EtOH	176.7	57.2	Pyridine-d <sub>5</sub>	21
						47.2 (227)	CH₃OH	7
	NHCH <sub>3</sub>	14	- 274.7	EtOH	181.3°	55.6 (273) <sup>a</sup>	Pyridine-d <sub>5</sub>	21
						45.1 (223) <sup>5</sup>	Pyridine-d <sub>5</sub>	21
						42.6 (203) <sup>b</sup>	CH₃OH	13
	NHC <sub>6</sub> H <sub>5</sub>	15				51.8 (253)	(CD <sub>3</sub> ) <sub>2</sub> CO	13
	NHCOCH <sub>3</sub>	16	-256.2	CDCl <sub>3</sub> /(CH <sub>3</sub> ) <sub>2</sub> CO	181.0ª	>82.3(>403)	DMSO-d <sub>6</sub>	13
	N(CH <sub>3</sub> ) <sub>2</sub>	17	-273.4	H <sub>2</sub> O/EtOH	182.8 <sup>c</sup>	50.6 (239)	(CD <sub>3</sub> ) <sub>2</sub> CO	13
(CH <sub>3</sub> ) <sub>2</sub> NCSX	NH <sub>2</sub>	17	- 275.2	H <sub>2</sub> O/EtOH	182.8 <sup>c</sup>	57.2 (268)	CH₃OH	13
	NHCH <sub>3</sub>	18	- 284.7	CDCl <sub>3</sub>	181.3	44.3 (211)	CDCl <sub>3</sub>	4
	NHC <sub>6</sub> H <sub>5</sub>	19		000		48.1 (231)	CDCl <sub>3</sub>	4
	$NHC_6H_4(CH_3)p$	20	-2/6./	CDCI3	182.6	47.2 (237)	CDCl <sub>3</sub>	4
	$N(CH_3)C_6H_4(NU_2)p$	21				34.7 (170)	CHFCI <sub>2</sub>	4
		22	005	000	404.0	67.3 (310)		39
	N(CH <sub>3</sub> ) <sub>2</sub> (TMTU)'	23	-285		194.0	26.3 (134)	CHFCI2/CHF2CI	41
	$N(CH_3)_2 + BF_3$		- 269.1"			43.9 (203)	CH <sub>2</sub> Cl <sub>2</sub>	22
	$(21M10+3BF_3)$		-278"	CDCI <sub>3</sub>				
(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> NCSX	N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	33	-256.2	CDCI <sub>3</sub>	193.7			
CH₃ <u>N</u> HCSX	NH₂	14	~275.2	СН₃ОН	181.3	∫61.4 (2 <del>9</del> 4)	Pyridine-d₅	21
						(63.1 (285)°	CH₃OH	8
	NHCH <sub>3</sub>	24	– 276.3 <sup>9</sup>	EtOH	181.0 <sup>c</sup>	≃48 <sup>r</sup>	CH₃OH	8
						52.2 (244) <sup>f</sup>	CD₃CN	12
	N(CH <sub>3</sub> ) <sub>2</sub>	18	- 278.8	CDCl3	181.3	44.3 (211)	CDCl <sub>3</sub>	4
$p(CH_3)C_6H_4NHCSX$	N(CH <sub>3</sub> ) <sub>2</sub>	20	-254.2	CDCl <sub>3</sub>	182.6			
C.H.NHCSX	NHC-H	25		CDCI		43 9 (215)	CDCI	20
061151110011	NHC_H_C(CH_)_0	34		02013		46.4 (214)		12
	11106140(013/30	•••					02013/(023/200	
CH₃CONHCSX	NH <sub>2</sub>	16	-217.6	CDCl <sub>3</sub> /(CD <sub>3</sub> ) <sub>2</sub> CO	181.0 <sup>d</sup>			
CH_CH_NHCSX	NH	26				59 3 (283)	Pyridine-d-	21
01130112111007	NH(CH_CH_)	27				48.9	Pyridine-d-	21
						-0.0	. ,	÷.,
(CH_)_CNHCSX	NHa	28				53.1	Pyridine-d-	21
	NHCH	29				48.9	Pvridine-d-	21
	NHC(CH_)	30	-241.3	CDCl	179.6	46.4	CH_CI_	13
				3			- 2-2	

Гэ	b	le	2.	Param	leters	s of	thioureas	(see	capti	ion	to	Table	1)	)
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<sup>a</sup> In isomer **14B** (CH<sub>3</sub> *trans* to CS). <sup>b</sup> In isomer **14A** (CH<sub>3</sub> *cis* to CS). <sup>c</sup> In methanol. <sup>d</sup> In dimethyl sulphoxide. <sup>e</sup> From **14B** (CH<sub>3</sub> *trans* to CS) to **14A** (CH<sub>3</sub> *cis* to CS). <sup>f</sup> The coalescence patterns are complex due to the existence of several conformational isomers. <sup>g</sup> Value of the <sup>15</sup>N—H coupling constant: 94.8 Hz. <sup>h</sup> Ref. 42. <sup>i</sup> TMTU is compound **23**.

#### **Conformational identification**

Identification of the conformational isomers in RR'N—CAR"(A = O, S) systems or assignments of the methyl signals in compounds of type  $(CH_3)_2NCAR"$  have been the subject of some controversy.<sup>30,31</sup> Although the low field methyl proton signal in amides and thioamides is frequently attributable to a methyl *cis* to the carbonyl<sup>30c</sup> there are numerous exceptions,<sup>30a,30b</sup> and the carbon spectrum is expected to provide a better criterion of conformational identification.<sup>30c,31</sup> In fact, the 250 MHz proton spectrum of the methyl group of urea **7** splits into two unequal doub-



lets at 250 K and the signal of higher intensity, *a*, appears at a lower frequency ( $\delta_{CH_3(a)} = 2.63$  ppm and  $\delta_{CH_3(b)} = 2.73$  ppm in methanol). Similarly, two unequal methyl carbon lines are separated at low temperature ( $\Delta \delta = 1.8$  ppm) and the stronger signal appears at a lower frequency. In spite of the rather unusual behaviour of the proton shifts, the isomer which predominates (87%) at 200 K is therefore given the structure **7A**, CH<sub>3</sub> *cis* to CO, on the basis of the <sup>13</sup>C shifts.

A different situation is encountered with the analogous thiourea 14. The <sup>1</sup>H signal of the methyl group splits into two doublets at 285 K ( $\Delta \delta \approx 0.2$  ppm in methanol) and two carbon signals, separated by 1.1 ppm in methanol, are also observed by lowering the temperature. On the basis of the signal intensities the low frequency proton methyl doublet is now associated with the high frequency carbon line and the slightly more abundant isomer at 213 K (55%) is given the structure CH<sub>3</sub> trans to CS.

Only one type of spectrum is observed for 16 and

the proton resonances of the  $NH_2$  group are not coalesced even at 403 K. This behaviour, along with the relatively low value of the <sup>15</sup>N screening is explained by the existence of a single conformational isomer in which a hydrogen of the  $NH_2$  group is engaged in a chelating interaction with the carbonyl oxygen.

# Nitrogen and carbon chemical shifts

The <sup>15</sup>N chemical shifts and the <sup>13</sup>C data for the carbonyl and thiocarbonyl carbons are given in Tables 1 and 2. It should be noted that a slight increase in screening ( $\simeq 1-1.5$  ppm) may be produced when the relaxation reagent  $Cr(acac)_3$  is added to the solution.<sup>24</sup> Moreover, variations in the nature of the solvent and in the concentration are capable of modifying the nitrogen chemical shifts significantly.<sup>43</sup> Thus  $|\delta^{15}N|$  of 1, which is 315.3 ppm in the neat compound, becomes 317.5 and 317.3 ppm in benzene and acetone ( $\simeq$ 20%), respectively. Unfortunately, because of sensitivity limitations, it was not possible to study dilute solutions in an inert solvent. Therefore, the possibility of substantial intermolecular effects must be kept in mind. Thus, relatively strong hydrogen bonding interactions between the carbonyl oxygen of ureas and protic solvents, for example, are expected. Similarly, self-association involving the NH and NH<sub>2</sub> groups of ureas are likely to produce significant effects. Different solvent contributions must, therefore, be taken into account when comparing the NH<sub>2</sub>, NHCH<sub>3</sub> and NR<sub>2</sub> systems. In order to obtain relatively comparable solvent effects within a series many compounds were studied in water-ethanol mixtures. Some of our <sup>15</sup>N chemical shift values are somewhat different from the corresponding <sup>14</sup>N shifts measured for certain ureas and thioureas.<sup>32,33</sup> In addition to solvent effects and different reference standards the quadrupolar broadenings of the <sup>14</sup>N signals are probably responsible for these discrepancies.

As regards <sup>13</sup>C spectroscopy, the carbonyl chemical shifts have been found, in several cases, to vary by less than 2 ppm when changing the solvent from CDCl<sub>3</sub> to CH<sub>3</sub>CN, (CH<sub>3</sub>)<sub>2</sub>CO, H<sub>2</sub>O and CH<sub>3</sub>OH.

# DISCUSSION

# Determination of the alkyl substituent effects in ureas and thioureas

It is interesting to examine the effects on  $\delta^{15}N$  of changing the nitrogen substituents R of compounds

$$R$$
 O, S  
N=C NR'R", with a given NR'R" group, and to

compare these effects with the corresponding variations measured in the amide series (Table 3). The increase in nitrogen screening observed when replacing a single hydrogen of  $NH_2$  by a methyl group is relatively insensitive to the nature of the NR'R" group and retains the same order of magnitude as in the amides ( $\approx 4-5$  ppm). More scattered variations accom-

Table 3. <sup>15</sup>N chemical shift differences due to the  $\alpha$  and  $\beta$  effects in ureas, thioureas and amides

	C'			
	N			
$\Delta \delta[N(R)_2] ppm$	"_ <sub>R"</sub>	Ureas	Amides	Thioureas
$\delta_{NHCH_2} - \delta_{NH_2}$	NH <sub>2</sub>	-3,6)		-4,5
5	NHCH <sub>3</sub>	-5,4	<b>≃</b> − <b>4</b>	-3,6
	N(CH <sub>3</sub> ) <sub>2</sub>	-6,2		-5,4
$\delta_{N(CH_2)_2} - \delta_{NH_2}$	NH <sub>2</sub>	-4,0		-4,5
12	NHCH <sub>3</sub>	-10,9		- 10,0
	N(CH <sub>3</sub> ) <sub>2</sub>	-11,7	≃-10	-11,6
	N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	- 10,7J		
$\delta_{N(CH_{2}CH_{2})_{2}} - \delta_{NH_{2}}$	NH <sub>2</sub>	+ 20,9		
	$N(\bar{CH}_3)_2$	+ 13,7	≃+ <b>24</b>	
	N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	+ 15,8		

pany the substitution of both hydrogens by alkyl groups. A source of these variations probably lies in the different steric interactions between the  $NR_2$ —NR'R'' and  $NH_2NR'R''$  groups. A regression analysis of the nitrogen chemical shift parameters was performed with a view to determining the substituent increments.

$$\delta_{15N(\text{ppm/NO}_3^{-})} = -300.7 + n'\alpha' + \sum_i n_i S_i$$
(1)

The  $\delta^{15}$ N values are expressed as a sum of structural contributions  $S_i$ , resulting from  $n_i(0, 1, 2, 3, 4)$  alkyl substitutions in the  $\alpha$ ,  $\beta$ ,  $\gamma'$  and  $\delta'$  positions

The n' term is a delta function having the value 0 for ureas and 1 for thioureas: the following values are calculated

$$\alpha' = 30.6(\pm 1), \ \alpha = -4.9(\pm 0.6), \ \beta = 14.3(\pm 0.7),$$
  
 $\gamma' = -2.4(\pm 0.6), \ \delta' = 0.8(\pm 0.5).$ 

These results are characterized by a multiple correlation coefficient of 0.99 and a standard deviation of  $\pm 2.6$  ppm. The Student's test on the  $\alpha'$  and  $\beta$  parameters have the greatest significance. No steric interaction has been considered in this treatment.

When comparing ureas with thioureas, an increase in the screening constant of about 30 ppm is observed (Tables 1 and 2). This effect is less than the 50 ppm increase measured in some amides and thioamides. Thus,  $\delta(CH_3)_2NCOR - \delta(CH_3)_2NCSR \approx -50$  ppm for R = H, Cl and  $\approx -47$  ppm for  $R = CH_3$ , for example. It is likely that the occurrence of low level excited states in thiocarbonyl compounds is responsible for most of the  $\delta^{15}N$  increment. Thus, to the extent that a mean excitation energy contribution may be considered,<sup>34</sup> a variation of 1 eV can be associated with a chemical shift of about 30 ppm.

#### Variations of the barrier to C—N rotation with structure in ureas and thioureas

Due to competitive conjugation and, possibly, to steric strain, the rotational barriers in ureas and thioureas

are always lower than in the corresponding amides. However, our results show that the lack of splitting at low temperature does not systematically result from very low activation energies. Several situations have to be actually considered. In unsymmetrically substituted compounds it is possible that only one conformational isomer is present in a detectable proportion. Such is probably the case for **5**, which is likely to exist in conformation **5A** as suggested by the small values of the  ${}^{4}J(\text{HH})$  and  ${}^{3}J({}^{15}\text{NH})$  coupling constants.<sup>35</sup> We



have also shown that a fortuitous equivalence, eventually maintained in several solvents, cannot be disregarded. Thus, no splitting of the alkyl signals has been observed down to 190 K for 3 and 4, even in aromatic solvents which are reputed to produce discriminating effects.<sup>5</sup> As relatively high values of the barrier are predicted on the basis of the correlations discussed below we have reinvestigated this problem and have succeeded, as already mentioned, in observing the decoalescence phenomena. In this respect it should be noted that proton chemical shift differences are often very small in ureas. Thus  $\Delta\delta NCH_3 = 0.04$  to 0.11 ppm in **1** when complexed with a Lewis acid,<sup>15,11</sup> 0.1 ppm in 7 and 0.02 and 0.05 ppm in the adducts of 3 and 4, respectively, with  $BF_3$ .<sup>5</sup> It is also of interest to note that an increase in the rotational barrier of about  $10 \text{ kJ mol}^{-1}$  is observed in thioureas as compared with ureas.

In order to obtain a better appraisal of the electronic and steric effects we have carried out some semi-empirical MO calculations. INDO calculations on various structures show that a planar form of **1** is more stable than a structure in which the methyl groups lie in a plane perpendicular to the remainder of the molecule. Although steric interactions between the methyls *trans* to C=A(A=O, S) introduce a distortion of the molecular framework, the rotational process still involves a nearly planar group state and a transition state in which an NR<sub>2</sub> group is perpendicular to the -CA-NR<sub>2</sub>' fragment.

# Relationship between the barrier to C-N rotation and the <sup>15</sup>N chemical shifts

We have pointed out that under certain conditions the nitrogen chemical shift of conjugated compounds can be correlated with the C—N rotational barriers.<sup>24-26</sup> As the  $\delta^{15}$ N parameter is much more easily accessible than an activation enthalpy, and can be measured for compounds in which exchange processes are not detectable, it is interesting to examine its ability to yield information about the nitrogen lone-pair delocalization in a given series.

Influence of alkyl substitution on  $\Delta G_T^{\dagger}$  and  $\delta^{15}N$ . In the

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series of ureas and thioureas 
$$N_1 - C_2 (\mathbf{R'R''})$$
 the

introduction of alkyl R', R" substituents is associated with an increase in the screening of N-1 and a decrease in  $\Delta G^{\ddagger}$ , as expected on the basis of a decreased conjugation.<sup>24</sup> These effects are relatively small for the

H<sub>2</sub><u>N</u>--C and CH<sub>3</sub><u>N</u>H--C fragments. Thus, in changing from R' = R'' = H to  $R' = R'' = CH_3$  the nitrogen signal of H<sub>2</sub><u>N</u>C moves to lower frequencies

by approximately 3 ppm for ureas and thioureas. By contrast, strong variations are observed in

(CH<sub>3</sub>)<sub>2</sub><u>N</u>—C—NR'R" molecules. An increase in screening by about 10 ppm and an important lowering of the  $\Delta G_T^*$  values is then observed for the nitrogen nuclei in the ureas and thioureas. Similarly, the formation of complexes between ureas or thioureas and Lewis acids such as BF<sub>3</sub>, SbCl<sub>5</sub> or TiCl<sub>4</sub> always produces a simultaneous increase in  $\delta^{15}$ N and  $\Delta G^*$  in accordance with an increase in the C—N double bond character. Diprotonation by means of 'magic acid' also introduces both a very large deshielding of the nonprotonated nitrogen and a strong enhancement of  $\Delta G^*(80 \text{ kJ mol}^{-1})$ .<sup>36</sup> Unfortunately, the results within a given series of similarly *N*-substituted ureas are too few for precise correlations to be deduced.

Influence of steric strain on the relationship between the  $\Delta G_T^{\dagger}$  and  $\delta^{15}N$  values. As ureas and thioureas are cross-conjugated compounds and steric interactions are likely to occur in N-substituted derivatives, the structural variations of  $\Delta G^{\dagger}$  should depend on both delocalization and steric effects. We have characterized the existence of steric interactions  $(I_S)$  by considering the number of  $\alpha$ -N and  $\gamma'$ -N substituents in the urea or thiourea studied and we have computed a multilinear regression for three independent variables  $\Delta G_T^{\dagger}$ ,  $\delta^{15}N_{corr}$  and  $I_S$ .  $I_S = n + n' - 1$  is a positive integer which has the following values

ureas: 
$$1378910$$
thioureas:  $131417182324$  $I_s: 310022$  $I_s: 0 0 1 2 3 1$ 

and  $\delta^{15}N_{corr}$  is the value of the nitrogen shift corrected for the  $\alpha$ ,  $\beta$  and  $\alpha'$  effect only (see above). It is interesting to note that correlations which are significant from a statistical point of view are obtained in this analysis: ( $\Delta G^{\ddagger}$  in kJ mol<sup>-1</sup> and  $\delta^{15}N$  in ppm/NO<sub>3</sub><sup>-</sup>)

ureas 
$$\Delta G_T^{\dagger} = 330.6 \pm 0.932 \,\delta^{15} \text{N} - 7.1 \,I_s$$
 (2)

The correlation is better for ureas (standard deviation for the  $\Delta G^{\ddagger}$  estimation = 2.9) than for thioureas (5.4) but the important point to note here is that Eqns (2) and (3) predict a decrease in the barrier height when the nitrogen shielding increases and when the steric interaction increases.

Thus, the orders of magnitude of the rotational barriers in compounds such as 3, 4 and 7(Z) could be successfully predicted on this basis. If the results concerning the ureas and thioureas are included in the previously published correlation for amides and thioamides<sup>24</sup> some anomalies appear. Thus, although the  $\delta^{15}N$  and  $\Delta G^{\ddagger}$  values in **1** corroborate an important decrease in the delocalization of the nitrogen lone pair, which probably originates from a distortion of the molecular framework under the effect of steric strain, the experimental  $\Delta G^{\ddagger}$  value of 26.3 kJ mol<sup>-1 37,41</sup> is lower than the  $\Delta H^{\ddagger}$  value predicted by the correlation.<sup>24</sup> If it is considered that, in the rotational transition state of (CH<sub>3</sub>)<sub>2</sub>NCANR'R", the observed (CH<sub>3</sub>)<sub>2</sub>N group is situated in a plane perpendicular to the carbonyl or thiocarbonyl plane, while the NR'R" group can be coplanar, the conjugation between NR'R" and CO or CS, which is possibly hindered by steric strain in the ground state, becomes fully allowed in the transition state. A decrease in the rotational barrier due to stabilization of the transition state can therefore be invoked.<sup>1</sup> However, this phenomenon is expected to affect all ureas or thioureas to a similar extent. In fact, Eqn (2) predicts a  $\Delta G^{\ddagger}$  value of 25.5 kJ mol<sup>-1</sup> for **1** which is very consistent with the experimental barrier  $(26.3 \text{ kJ mol}^{-1})$ . It should be stressed that in this treatment 1 is characterized by a high  $I_{S}$  value which denotes important steric hindrance. It is interesting to note that if we ignore this steric contribution Eqn (2) predicts a value  $(46 \text{ kJ mol}^{-1})$  which is comparable with that given by using Eqn (1) of Ref. 24. As regards the origin of the different responses of  $\delta^{15}N$  and  $\Delta G_T^{\ddagger}$  to steric contributions, is should be noted that a decrease in the mean excitation energy due to rotational effects in crowded structures such as 1 and 23 is liable to introduce a deshielding effect which would partially compensate for the increase in shielding associated with the increased localization of the lone pair. In this respect it should be noted that similar behaviour is observed for the crowded amide, (CH<sub>3</sub>)<sub>2</sub>NCOC(CH<sub>3</sub>)<sub>3</sub>. By contrast, when substituted on the H<sub>2</sub>NCO fragment, the *t*-butyl group introduces less steric strain and the  $\delta^{15}N$  experimental value then agrees more closely with that predicted.42

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