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ON THE STRUCTURE OF THIOAMIDES AND THEIR DERIVATIVES—XXI[1]

TEMPERATURE DEPENDENCE IN THE NMR SPECTRA OF UREA, THIOUREA, AND SELENOUREA

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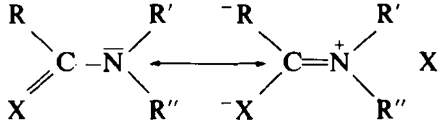
Abstract In the low-temperature NMR spectra of urea (I), thiourea (II), and selenourea (III) two resonances were observed and could be assigned to the inner and outer protons. With the aid of ^{14}N decoupled ^{1}H-NMR spectra the barriers to internal rotation in I–III could be obtained. The barrier height is influenced by the hydrogen bonding ability of the solvent.

INTRODUCTION

NMR SPECTROSCOPY HAS PROVEN to be a powerful tool in the study of effects connected with hindered internal rotation in secondary and tertiary amides and in the analogous thio and seleno compounds, which are planar due to electron delocalization:[2, 3]

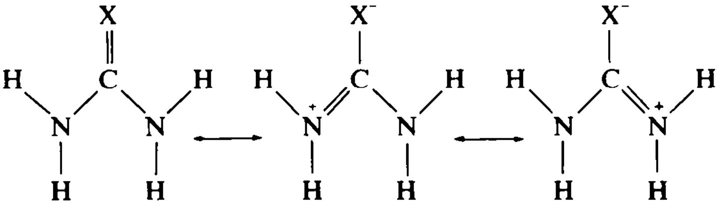


X = O, S, Se

However, for (thio)amides unsubstituted at nitrogen ($R' = R'' = H$), nonequivalence of the N—H protons cannot usually be detected because of quadrupole broadening of the hydrogen resonances. The difficulties arising from the influence of the ^{14}N nucleus on the rate of proton relaxation have been overcome by the introduction of the ^{15}N isotope[4, 5] or by magnetic saturation of the ^{14}N resonance absorption.[4] For formamide ($R = R' = R'' = H$) it has been shown using both techniques that internal rotation is hindered at room temperature on the NMR time scale ($\Delta G^{\ddagger} = 17{\cdot}8$ kcal/mole in diglyme).[4] A different situation is to be expected for urea and its homologues, where several influences will tend to lower the rotational barrier:

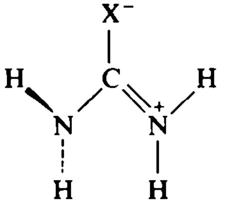
(a) Replacement of the formyl hydrogen in formamide by the amino group will raise the steric strain in the planar ground state and thus increase its energy.

(b) The lone electron pairs on both nitrogen atoms compete in the mesomeric interaction with the sulphur orbitals producing in each half of the molecule a weaker partial double bond than in formamide.



I: X = O
II: X = S
III: X = Se

(c) When one amino group is turned out of the plane of the molecule during the rotational process, undisturbed mesomerism in the other half of the molecule is possible and thus the energy of the transition state is lowered:



Until now, quantitative data of the barrier height have been available only for urea.[6] Therefore in order to evaluate the effects of the influences (a)–(c) and of the substituent X on the barrier height, a detailed investigation of urea (I), thiourea (II), and selenourea (III) was carried out.

RESULTS AND DISCUSSION

Spectra. Beside internal rotation another dynamic process which is possible in urea and its homologues is proton exchange. This exchange can be suppressed by the formation of strong hydrogen bonds. Therefore a mixture of dimethylformamide (DMF) and acetone was chosen as the solvent for this study, in which the compounds in question proved to be sufficiently soluble and which has a low enough freezing-point.

At the normal temperature of 35°C compounds I–III gave rather broad proton resonances with line-widths at one-half height of 20–100 Hz, in which a triplet structure caused by coupling with the ^{14}N nucleus ($I = 1$) could not be detected. On irradiation of the sample with the ^{14}N resonance frequency found by changing the double resonance frequency until the shape of the proton spectrum was optimal, the quadrupole broadening could be removed. The NH_2 absorption of each compound studied appeared then as a single sharp line with a line-width at one-half height of about 4 Hz, as is shown for II in Fig. 1. This behaviour shows that proton exchange does not contribute significantly to the broad signals observed without ^{14}N irradiation, probably because, as desired, hydrogen bonding with the solvent makes proton exchange slow on the NMR time scale.

At low temperatures ($-80°C$ for I, $-70°C$ for II and III) instead of a single peak two sharp resonances with linewidths of about 5 Hz were observed even without ^{14}N irradiation, as has previously been reported for I[6] and II.[7] Obviously, internal

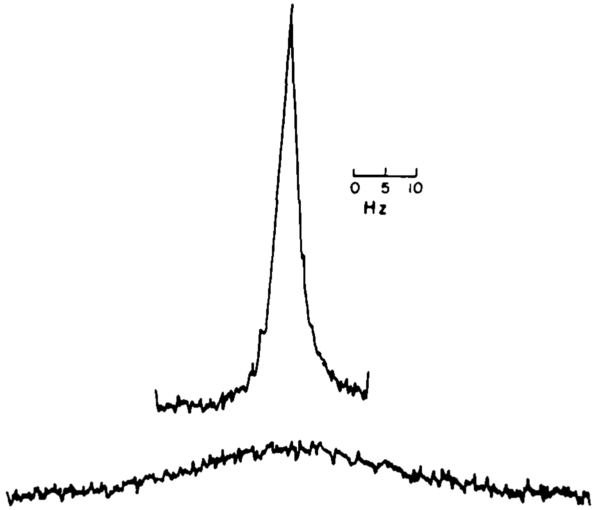
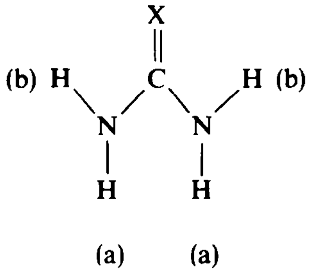


FIG. 1. Proton resonance spectrum of thiourea (II) without (below) and with ^{14}N decoupling (above) in acetone-d_6 at 35°C.

rotation is considerably hindered at these temperatures and the two peaks are due to the two equivalent inner (a) and outer (b) hydrogens of the urea system respectively:



^{14}N irradiation at low temperatures ($< -40°$) does not change the appearance of the proton resonance spectrum. In fact, on cooling below ordinary temperatures the ^{14}N resonance frequency becomes increasingly less well defined indicating a broadening of the ^{14}N signal, while the proton signals sharpen even without ^{14}N decoupling and the effect of ^{14}N irradiation becomes less striking. This behaviour is in agreement with a theory outlined by Pople[8,9] according to which a nucleus of spin $\frac{1}{2}$ and one of spin 1 will couple in the absence of quadrupole relaxation. The multiplets will broaden, however, if the rate of quadrupole relaxation is slow, and for rapid relaxation the two nuclei will be decoupled; the spectrum of the nucleus of $I = \frac{1}{2}$ consisting of a sharp line and the spectrum of the nucleus of $I = 1$ showing a very broad signal. Obviously, on cooling and thus increasing the spin-lattice relaxation time (T_1) these changes in the rate of proton relaxation are observed for the compounds studied.

Not only the shape of the proton peaks, but also the chemical shift is affected by cooling. Both signals observed when chemical exchange is slow move downfield on lowering the temperature, the high-field peak being shifted more slowly than the low field-peak relative to the formyl resonance of the solvent. Thus the peak separation $\Delta\nu$ increases on cooling (Table 1), apparently because hydrogen bonds of different strength are formed with the inner (a) and outer (b) protons of I–III. In secondary (thio)formamides stronger hydrogen bonds are formed with the proton *trans* to the sulphur atom, because solvation of the *cis* position is electrostatically and sterically less favoured.[10] In the urea system, however, the inner (a) or *trans* protons are quite close to each other so that at a time only one of these protons will enter into a hydrogen bond. Alternatively, a bifurcated hydrogen bond can be expected. This is why the resonance observed at lower field in I–III is assigned to the outer protons (b). This assignment is supported by the results of benzene dilution experiments. Using this technique, signals from protons *trans* to oxygen, sulphur or selenium are shifted upfield, because the collision complex with benzene is electrostatically more favoured in the *trans* position. It has been shown that this method, which was previously developed for amides,[11] can also be applied to thioureas.[12] For the compounds in question, benzene dilution should lead to a larger peak separation $\Delta\nu$, if the conclusions derived from the assumed hydrogen bonding are correct. In fact, this behaviour is observed for II and III (Table 1), (urea (I) was not sufficiently soluble in the presence of benzene).

Table 1. Peak separation, $\Delta\nu$, in DMF$(-d_7)$/acetone-d_6 and after dilution with a tenfold molar excess of benzene-d_6 relative to II or III at different temperatures

	−40°	−50°	−60°	−65°	−70°	−80°	−90°	
I	—[a]	—[a]	32	37·5	—[b]	49	—[c]	cps
II	25	32·5	38	—[b]	42	47	—[c]	cps
+C_6D_6	—[b]	34	40	42	44	—[c]	—[c]	cps
III	20	26	30·5	32·5	35	38	40	cps
+C_6D_6	24	29	34	—[b]	39	—[c]	—[c]	cps

[a] Temperature above or near coalescence
[b] Not measured
[c] Crystallization of the sample occurs

The assignment of the low-field resonance to the *cis* position in II and III is in agreement with the results obtained for primary thioamides,[13, 14] but the shielding conditions for I are contrary to those in formamide.[15] However, this is obviously due to the influence of the solvent, which obscures the effects of intramolecular diamagnetic anisotropy.

Barrier heights. From the coalescence of the two signals observed at low temperatures the free enthalpies of activation $\Delta G^\ddagger$ for hindered internal rotation can be obtained.[2, 3] For the calculation of the rate constant at the coalescence temperature T_c, the constant value of the peak separation in the absence of chemical exchange is necessary. However, as is evident from table 1, the slow exchange limit of $\Delta\nu$ cannot be measured, since the difference of chemical shifts is affected by the temperature dependance of hydrogen bonding (*vide supra*). Therefore a somewhat arbitrary value of $\Delta\nu$ must be chosen, here the $\Delta\nu$ obtained at −80° for I (the lowest temperature reached), and −70° for II and III, i.e. about 50° below T_c, (Table 1). The error, which may be introduced by this procedure is not serious, because, as has been pointed out previously,[16] an error of 50% in $\Delta\nu$ produces only minor variations in $\Delta G^{\ddagger}$.

For the case of slow rotation, the magnetically nonequivalent hydrogen atoms (a) and (b) in I–III should be coupled and appear as doublets. In fact, this behaviour is observed for primary thioamides, which already show restricted rotation at ordinary temperatures.[13] For I–III, however, this coupling could not be resolved probably because of residual quadrupole broadening.

If J_{AB} is assumed to be 3·5 Hz (the value obtained for thioacetamide in DMF-d_7/acetone-d_6) and the rate constant is calculated for the coalescence of an AB quadruplet,[17] the values of $\Delta G^{\ddagger}$ do not change noticeably, since the peak separations $\Delta\nu$ are comparatively large in I–III.

Whereas coalescence is not perceptibly affected by quadrupole relaxation effects in urea (I) because of the low T_c, in II and III quadrupole broadening produces a value of T_c which is too low, for T_c is raised 4–7° by ^{14}N irradiation and consequently $\Delta G^{\ddagger}$ 0·2–0·4 kcal/mole.

The calculated barrier heights $\Delta G^{\ddagger}$, which because the molecules are symmetrical, refer to rotation around both C—N bonds, are compiled in Table 2. An inspection of the table reveals that on passing from I to II $\Delta G^{\ddagger}$ markedly increases suggesting a stronger contribution of the polar canonical forms in thiourea (II) than in urea (I). The same has been deduced from the difference in barrier heights between amides and thioamides, where usually differences of 3–4 kcal/mol are found.[18] The difference in $\Delta G^{\ddagger}$ between I and II is much less pronounced, indicating that the competing mesomeric interactions tend to level the barrier heights between the oxygen and the thio compound. This tendency leads to the unexpected result that no difference in the rotational barriers of II and III in DMF/acetone could be detected. In other instances[19,20] it has been shown that the changes between thio- and selenoamides are smaller than those between amides and thioamides, but that they are still significant. To explain these results it has been suggested that in the seleno compounds steric interactions in the ground state are stronger because of the larger size of selenium compared to sulphur and consequently the electronic effect of selenium is at least partially compensated.[19]

TABLE 2. PEAK SEPARATIONS, $\Delta\nu$ (CORRECTED FOR $J_{AB} = 3{\cdot}5$ HZ), COALESCENCE TEMPERATURES, T_c, AND FREE ENTHALPIES OF ACTIVATION, $\Delta G^{\ddagger}$, FOR I–III

	X	solvent	$\Delta\nu$[Hz]	T_c[°C]	$\Delta G^{\ddagger}$[kcal/mole]
I	O	DMF/acetone[a]	48	−48	11·0
II	S	DMF/acetone[a]	41	−14	12·8
		DMF-d_7(3 mole-% II)	43	−9	13·0
		acetone-d_6(1 mole-% II)	30	−11	13·1
		MeCN (1 mole-% II)	29	−33	12·0
III	Se	DMF-d_7/acetone-d_6[a]	34	−16	12·8

[a] Concentration: 0·07 mMole I, II, or III in 4 mMole DMF (-d_7) and 4 mMole acetone-d_6

It is interesting to compare the barrier height for II with those reported for

N-methylthiourea. The results obtained for this compound ($\Delta G^\ddagger = 15{\cdot}1$ kcal/mole for rotation around the $CH_3NH—CS$ bond, and 10·2 kcal/mole for the $CS—NH_2$ bond, in MeOH)[21] indicate that the effect of competing mesomerism can at least partially be neutralized by the introduction of one Me Group, and thus making the urea system assymmetric. The calculated "medium $\Delta G^\ddagger$ value" of 12·7 kcal/mole for N-methylthiourea is not higher than the barrier height for II, which would be expected owing to the inductive effect of the alkyl group in analogy to thioamides.[10] This could be due to the different solvents used in this study. The activation enthalpy obtained for III has a special significance when compared with the result of Jensen and Sandström that tetramethylselenourea gives only one signal down to $-120°$ ($\Delta G^\ddagger < 7{\cdot}9$ kcal/mole).[19] The much larger value for III (Table 1), which cannot be ascribed only to hydrogen bonding effects, suggests that the low barrier height of the methylated compound must be due to steric strain in the ground state, where the two dimethylamino groups cannot be planar, for, if so, the effect of competing mesomerism would be similar to that in II.

Although only a very limited range of solvents could be used for I due to its low solubility,[6] thiourea (II) is somewhat more suitable for studying the solvent dependance of $\Delta G^\ddagger$. The difference between the $\Delta G^\ddagger$ values in pure DMF and in pure acetone is negligent (Table 1). In MeCN, however, T_c is significantly lower than in DMF/acetone and the peak separation is smaller. At the lowest temperature reached in this solvent ($-45°$) $\Delta\nu$ is only 12 Hz compared with about 20 Hz for II in DMF/acetone at 12° below T_c. Assuming a peak separation of 30 Hz for slow exchange, $\Delta G^\ddagger$ is nearly 1 kcal/mole lower than in DMF/acetone (Table 1), though MeCN is more polar than DMF or acetone[22] and might lower the energy of the polar ground state by better solvation. The opposite behaviour can be explained by the stronger hydrogen bonding ability of DMF and acetone, because of which an additional amount of energy is required for the rotational process, since hydrogen bonds must first be broken, or, in other words, the ground state of rotation is stabilized by hydrogen bonding.

EXPERIMENTAL

I–III were commercially available. Selenourea (III) was recrystallized from EtOH prior to use. NMR spectra were recorded using a Varian HA 100 spectrometer and a Varian V-4343 variable temperature equipment. TMS was used as the internal standard. Temperatures were measured with the aid of the chemical shifts of the MeOH spectrum. The details of the ^{14}N decoupling equipment have been described previously.[23]

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