

^{15}N , ^{13}C , AND ^1H NMR SPECTRA OF ACYLATED UREAS AND THIOUREAS

Josef JIRMAN and Antonín LYČKA

Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitví

Received January 8th, 1987

A series of 1-acylated and 1,3-diacylated (acyl = acetyl or benzoyl) ureas and thioureas have been prepared and their proton-coupled and proton-decoupled ^{15}N , ^{13}C , and ^1H NMR spectra have been measured. All the signals have been assigned. The ^{15}N NMR chemical shifts in 1-acylated ureas and thioureas are shifted downfield as compared with $\delta(^{15}\text{N})$ of urea and thiourea, resp. This shift is greater for N-1 than for N-3 nitrogen atoms in both the series. When comparing acylureas and acylthioureas it is obvious from the $\Delta\delta(^{15}\text{N})$ differences that the CS group is better than CO group in transferring the electron-acceptor effect of acyl group. The proton-coupled ^{15}N NMR spectra of the acylureas dissolved in hexadeuteriodimethyl sulphoxide exhibit a doublet of NH group and a triplet of NH_2 group at 25°C. At the same conditions the acylthioureas exhibit a doublet of NH group, the NH_2 group signal being split into a doublet of doublets with different coupling constants $^1J(^{15}\text{N}, \text{H})$. The greater one of these coupling constants is due to the *s-trans* proton with respect to the sulphur atom of the thiourea.

Acylureas and acylthioureas have continued to be described in literature for almost a hundred years. Many papers¹⁻⁴ deal with the acylation position in ureas and thioureas. Two such positions are available in symmetrical ureas and thioureas (N, O and N, S, respectively) and three positions in the unsymmetrical ones (N-1, N-3, O (or S)). Structure of acylated ureas and thioureas was proved indirectly by means of various chemical reactions, hence the conclusions made by the individual authors about structure of these compounds are differing.

The aim of this work was an unambiguous differentiation between the individual acylation positions in ureas and thioureas. The ^{15}N NMR spectroscopy was used for this purpose, as it enables to determine the number of magnetically non-equivalent nitrogen atoms in the molecule and differentiate between the N, NH, and NH_2 groups on the basis of the coupling constants $^1J(^{15}\text{N}, \text{H})$ found from the proton-coupled ^{15}N NMR spectrum. In our opinion, the ^{15}N NMR spectroscopy represents the most advantageous method for verification of structure of acylated ureas and thioureas in solution.

EXPERIMENTAL

Measurements of NMR Spectra

The ^1H , ^{13}C , and ^{15}N NMR spectra were measured at 99.602 MHz, 25.047 MHz, and 10.905 MHz, respectively, by means of a JNM-FX 100 (JEOL) apparatus at 25°C. The ^1H NMR spectra of compounds *I* through *X* were measured in about 0.5 mol dm⁻³ solutions in hexadeuteriodimethyl sulphoxide. The ^1H chemical shifts are related to internal tetramethylsilane ($\delta = 0.00$). The ^{13}C and ^{15}N NMR spectra were measured in hexadeuteriodimethyl sulphoxide solutions (saturated at 25°C). The ^{13}C NMR chemical shifts are related to internal tetramethylsilane ($\delta = 0.0$). The ^{15}N NMR chemical shifts are related to external nitromethane (25% ^{15}N , $\delta = 0.0$). Negative values of chemical shifts denote upfield shifts. The parameters of measurements: the proton-decoupled ^{15}N NMR spectra: 5 000 Hz spectral width, 8 K, 45° pulse, 3.5 s pulse repetition, 1 000 to 3 000 pulses; the proton-coupled ^{15}N NMR spectra: 2 000 Hz spectral width, 8 K, 60° pulse, 8 s pulse repetition, 4 000 to 6 000 pulses, gated decoupling. The assignment of ^1H chemical shifts of the acidic protons in compounds *VI* and *X* was carried out by the method of selective decoupling of the NH protons in the measurement of ^{15}N NMR spectrum with an AM 400 (BRUKER) apparatus at 44.55 MHz. On the same spectrometer we also measured the ^{13}C selective INEPT with compound *V* at 100.61 MHz. The experiment was optimized at the presumed magnitude of the coupling constant $^2J(\text{C}, \text{NH})$ of about 6 Hz according to ref.⁵.

Chemicals

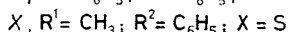
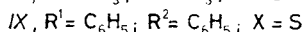
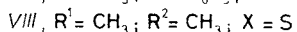
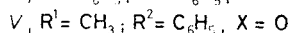
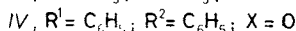
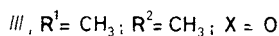
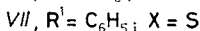
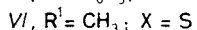
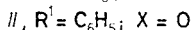
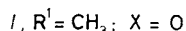
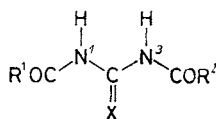
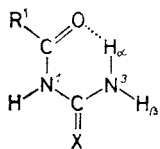
1-Acetylurea¹ (*I*), 1-benzoylurea² (*II*), 1,3-diacetylurea³ (*III*), 1-acetylthiourea¹ (*VI*), 1-benzoylthiourea⁴ (*VII*), 1,3-diacetylthiourea¹ (*VIII*), and 1,3-dibenzoylthiourea⁶ (*IX*) were prepared according to the literature data. 1,3-Dibenzoylurea (*IV*) was prepared from benzoyl isocyanate⁷ and benzamide by a procedure analogous to that described in ref.⁸. The product was recrystallized from an ethanol-chloroform-xylene mixture (2 : 1 : 1) to give white needles melting at 188–190°C in accordance with ref.⁹. 1-Acetyl-3-benzoylthiourea (*X*) was prepared by acetylation of 1-benzoylthiourea (*VII*) with acetanhydride according to ref.¹⁰.

1-Acetyl-3-benzoylurea (*V*). 19 g (0.32 mol) urea and 45 g (0.32 mol) benzoylchloride were mixed with 100 ml dried acetone and refluxed 10 min. After cooling, the separated crystals were collected by suction and heated on an oil bath at 160°C 1 h. After cooling, 60 ml acetanhydride and 3 ml conc. sulphuric acid were added. The mixture was heated at 100–115°C 10 min. After cooling, the separated crystals were collected by suction and washed with acetone. The product was recrystallized from ethanol, m.p. 185–186°C (ref.¹¹ gives m.p. 187°C). Yield 15.8 g (24%).

RESULTS AND DISCUSSION

The preparation of N-acylated ureas and thioureas is relatively simple. Compounds *I* and *VI* were prepared by acylation of urea and thiourea, resp., with acetanhydride¹. Compounds *II* and *VII* were prepared by acylation of urea and thiourea, resp., with benzoyl chloride^{2,4}. However, the acylation to the second degree is more difficult. The preparation of diacetyl derivatives *III* and *VIII* was studied earlier^{1,3,12}. Non-symmetrical diacylureas can be prepared by the condensation of acylisocyanate with the corresponding amide^{8,11}. In this work, the non-symmetrical diacylurea *V*

was prepared by stepwise acylation, the acylation to the second degree being accomplished by application of the anhydride with the lower-molecular acyl group than that present in the monoureide (in analogy to the work by Stoughton¹² who used the acyl chloride as the acylating agent). For non-symmetrical diacylthioureas no procedures starting from acyl isothiocyanates and amides are described in literature. Therefore, acylation of compound *VII* (ref.¹⁰) was used for preparation of compound *X*. But this method is not advantageous, since acylthioureas can undergo transacylation reactions in the presence of an acylating agent^{6,10}, hence compound *X* is not the main product. The yield of compound *X* was not increased by excess acetanhydride or increased amount of pyridine (used as medium) or by addition of sulphuric acid as a catalyst. On the other hand, the transacylation reaction was utilized in the preparation of 1,3-dibenzoylthiourea *IX* from compound *VIII* and benzoyl chloride^{6,10}. As the transacylation does not take place with acylureas¹³, 1,3-dibenzoylurea (*IV*) was prepared by a modified procedure of ref.⁸.



The ¹H NMR chemical shifts of NH groups of compounds *I* through *X* are given in Table I. The acylureas and acylthioureas, dissolved in hexadeuteriodimethyl sulphoxide at 25°C, assume a cyclic form similar to that of acylureas in deuteriochloroform solutions¹⁴. This finding was confirmed by dilution experiments: heavy water was added drop by drop to solutions of compounds *VI* and *VII* in hexadeuteriodimethyl sulphoxide. The intensity of signals of NH protons was gradually decreased. Immediately after addition of ²H₂O, the H-1 signal had a lower intensity (by about 1/3) than the H-3 protons. Within 10 min the intensity of signals of all three protons became equal. On addition of heavy water, the signals of two NH protons were not only decreased in their intensity but also shifted upfield. One of the H-3 protons gave a signal at a constant field independent of the water additions. This signal was assigned to the H_α proton which forms an intramolecular hydrogen bond with the acyl carbonyl. The proton signals and ¹J(¹⁵N, H) coupling constants of compound *VI* were assigned on the basis of the measurements of ¹⁵N NMR

TABLE I

The ^{15}N , ^1H , and ^{13}C chemical shifts and $^1J(^{15}\text{N}, \text{H})$ coupling constants of compounds I through X dissolved in hexadeuteriodimethyl sulphoxide (25°C)

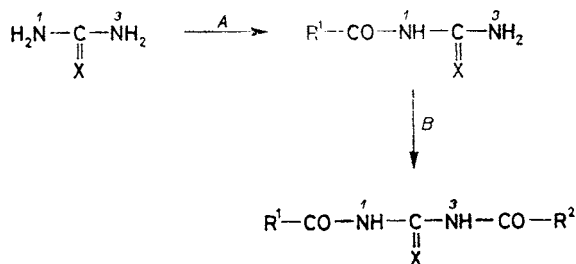
| Compound | I | II | III | IV | V | VI | VII | VIII | IX | X |
|---|--------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| $\delta(^{15}\text{N}-1)$ | -230.7 | -237.6 | -230.5 | -237.3 | -228.2 | -217.5 | -224.0 | -210.7 | -216.9 | -207.6 |
| $\delta(^{15}\text{N}-3)$ | -292.6 | -291.2 | -230.5 | -237.3 | -239.8 | -254.3 | -253.1 | -210.7 | -216.9 | -221.2 |
| $^1J(^{15}\text{N}-1, \text{H})$ | 89.8 | 89.6 | 88.1 | - ^a | - ^a | 92.3 | - ^b | 89.1 | 89.6 | 92.2 |
| $^1J(^{15}\text{N}-3, \text{H})$ | 89.6 | 90.3 | 88.1 | - ^a | - ^a | 93.6 ^c | 94.2 ^c | 89.1 | 89.6 | 86.1 |
| $\delta(\text{H}_\alpha)$ | 7.8 | 8.1 ^e | 10.9 ^f | 11.9 ^f | 11.8 ^f | 88.6 ^d | 88.4 ^d | 12.3 ^f | 12.1 ^f | 13.7 ^f |
| $\delta(\text{H}_\beta)$ | 7.2 | 7.5 ^e | - | - | - | 9.6 | 9.9 | - | - | - |
| $\delta(\text{H}-1)$ | 10.2 | 10.6 | 10.9 | 11.9 | 11.1 | 11.0 | 11.2 | 12.3 | 12.9 | 12.0 |
| $\delta(^{13}\text{C}(\text{CH}_3 \text{ CO}))$: CH_3 | 23.8 | - | 24.7 | - | 24.5 | 23.7 | - | 25.5 | - | 24.2 |
| $\delta(^{13}\text{C}(\text{CH}_3 \text{ CO}))$: CO | 172.4 | - | 172.6 | - | 173.2 | 172.2 | - | 171.6 | - | 172.9 |
| $\delta(^{13}\text{C}(\text{C}_6\text{H}_5 \text{ CO}))$: C_i | - | 132.9 | - | 132.6 | 132.7 | - | 132.3 | - | 132.6 | 133.3 |
| C_o | - | 128.3 | - | 128.1 | 127.8 | - | 128.5 | - | 128.5 | 127.7 |
| C_m | - | 128.6 | - | 129.1 | 129.1 | - | 128.4 | - | 128.8 | 129.3 |
| C_p | - | 132.9 | - | 133.5 | 133.4 | - | 133.0 | - | 133.4 | 133.4 |
| CO | - | 168.3 | - | 166.9 | 165.9 | - | 167.7 | - | 166.4 | 164.5 |
| $\delta(^{13}\text{C}(\text{CX}))$ | 154.4 | 154.5 | 150.1 | 149.1 | 149.3 | 181.9 | 182.2 | 179.0 | 179.2 | 178.5 |

^a The $^1J(^{15}\text{N}, \text{H})$ value could not be measured by the 16 h accumulation of spectrum because of lower solubility of the substance in hexadeuteriodimethyl sulphoxide; ^b $^1J(^{15}\text{N}-1, \text{H})$ was not observed due to the rapid proton exchange at N-1 nitrogen atom; ^c $^1J(^{15}\text{N}-3, \text{H}_\alpha)$; ^d $^1J(^{15}\text{N}-3, \text{H}_\beta)$; ^e the values of chemical shifts are approximative, the signals were overlapped by the absorption of aromatic protons; ^f $\delta(\text{H}-3)$.

spectra with selective irradiation of the proton signals with a constant decoupling power and by comparison of the residual coupling constants. The H-1 and H-3 protons of compound *V* were assigned by application of the selective INEPT technique⁵ with respect to known chemical shifts of carbonyls in acetyl and benzoyl (see Table I). The assignment of the ¹³C chemical shifts of the acetyl and benzoyl carbonyl groups is given below. After excitation of the NH proton with the lower-field signal, the ¹³C selective INEPT spectrum exhibited a signal with $\delta = 165.9$ due to C₆H₅CO carbonyl, on the other hand, after excitation of the higher-field NH proton a signal was observed at $\delta = 173.2$. As the selective INEPT was optimized according to ²*J*(¹³C, NH), the above results allow an unambiguous assignment of the ¹H chemical shifts of the NH protons. The assignment of the NH proton signals of compound *X* was carried out on the basis of selective heteronuclear decoupling during measurements of the ¹⁵N NMR spectra.

The ¹³C NMR chemical shifts of compounds *I* through *X* are given in Table I. The signals of CO and CS groups were differentiated on the basis of the appearance of the spectrum with retained ⁿ*J*(C, H) coupling constants (*n* ≥ 1). The acetyl carbonyls in this spectrum show a broadened quartet, the benzoyl carbonyls show a broadened triplet. The signals of CO and CS groups of ureide and thioureide type, resp., show a singlet at these measurement conditions.

The ¹⁵N NMR chemical shifts of nitrogen atoms of the acylated ureas *I* through *V* and thioureas *VI* through *X* are given in Table I. Saturated solutions of thiourea and urea in hexadeuteriodimethyl sulphoxide at 25°C show the ¹⁵N NMR signals at -271.0 and -302.8 ppm, resp. The acylation of urea and thiourea to the first degree (Scheme 1, reaction (A)) is accompanied by shielding of both nitrogen atoms.



SCHEME 1

This shielding will cause a downfield shift of the two nitrogen atoms as compared with the ¹⁵N NMR signals of urea and thiourea, resp. The difference in chemical shifts of N-1 atoms of acylureas *I* and *II* and acylthioureas *VI* and *VII* is comparable with the difference in the ¹⁵N NMR chemical shifts of N-methylamides of acetic and benzoic acids¹⁵. The magnitude of shielding of the nitrogen atoms by the acyla-

tion is expressed in Table II as $\Delta\delta(^{15}\text{N}(\text{CX})_A)$ calculated from Eq. (1)

$$\Delta\delta(^{15}\text{N}(\text{CX})_A) = U - M, \quad (1)$$

where $U = \delta(^{15}\text{N})$ of urea ($\text{X} = \text{O}$) and thiourea ($\text{X} = \text{S}$), resp., and $M = \delta(^{15}\text{N})$ of the monoacyl derivative (after the reaction (A)). The downfield shift of the N-1 nitrogen signals due to the acylation to the first degree (Scheme 1, reaction (A)) is greater for $\text{X} = \text{O}$ than for $\text{X} = \text{S}$, hence the difference (2)

$$\Delta\delta(^{15}\text{N}(\text{CO})_A) - \Delta\delta(^{15}\text{N}(\text{CS})_A) \quad (2)$$

has the values 18.6 and 18.1 for the acetyl and benzoyl derivatives, resp. The opposite situation is observed for the N-3 nitrogen atoms, the above difference (2) being negative (-6.5 and -6.3 for the acetyl and benzoyl derivatives, resp.). Therefrom it follows that CS is better than CO group in transmitting the electron-acceptor effect of acyl group to N-3 atom. The same effects as those mentioned for the reaction (A) are also operating in the acylation to the second degree (Scheme 1, reaction (B)). The shielding values are given in Table III as $\Delta\delta(^{15}\text{N}(\text{CX})_B)$ calculated from Eq. (3)

$$\Delta\delta(^{15}\text{N}(\text{CX})_B) = M - D, \quad (3)$$

where $M = \delta(^{15}\text{N})$ of the monoacyl derivative (before the reaction (B)) and $D = \delta(^{15}\text{N})$ of the diacyl derivative (after the reaction (B)). A formal difference only consists in that now the difference values are negative (expression (4))

$$\Delta\delta(^{15}\text{N}(\text{CO})_B) - \Delta\delta(^{15}\text{N}(\text{CS})_B) \quad (4)$$

for the N-1 atoms, *i.e.* the nitrogen atoms acylated in the first step. The results are summarized in Table IV. These results can be explained by the CS group of acylthioureas being more efficient than the CO group of acylurcas in lowering the electron density at both the nitrogen atoms, which can be documented, *e.g.*, by higher acidity of NH protons in benzoylthioureas as compared with their oxygen analogues¹⁶.

When measuring the ^{15}N NMR spectra with retained $^1J(^{15}\text{N}, \text{H})$ coupling constants we observed no dependence between the magnitude of coupling constants and type or number of acyl groups. For compounds IV and V the $^1J(^{15}\text{N}, \text{H})$ coupling constants could not be measured due to lower solubility of the compounds in hexadeuteriodimethyl sulphoxide. With compound VII the $^1J(^{15}\text{N}, \text{H})$ coupling constant repeatedly was not observed at the N-1 atom due to exchange of the H-1 proton with traces of water present in the solvent which was used without any special pre-drying. For comparison we also measured the $^1J(^{15}\text{N}, \text{H})$ coupling constants of urea (87.2 Hz) and thiourea (90.8 Hz). The acyl-

TABLE II

The ^{15}N substituent chemical shifts^a $\Delta\delta(^{15}\text{N}(\text{CX})_A)$ found after introduction of the first acyl group (Scheme 1, equation (A))

| R ¹ | X = O | | X = S | |
|-------------------------------|-------|------|-------|------|
| | N-1 | N-3 | N-1 | N-3 |
| CH ₃ | 72.1 | 10.2 | 53.5 | 16.7 |
| C ₆ H ₅ | 65.2 | 11.6 | 47.1 | 17.9 |

^a See Eq. (1).

TABLE III

The ^{15}N substituent chemical shifts^a $\Delta\delta(^{15}\text{N}(\text{CX})_B)$ found after introduction of the second acyl group (Scheme 1, equation (B))

| R ¹ | R ² = CH ₃ | | | | R ² = C ₆ H ₅ | | | |
|-------------------------------|----------------------------------|------|-------|------|--|------|-------|------|
| | X = O | | X = S | | X = O | | X = S | |
| | N-1 | N-3 | N-1 | N-3 | N-1 | N-3 | N-1 | N-3 |
| CH ₃ | 0.2 | 62.0 | 6.9 | 43.7 | 2.5 | 59.8 | 9.9 | 33.1 |
| C ₆ H ₅ | -2.2 | 63.0 | 2.8 | 45.5 | 0.3 | 53.9 | 7.1 | 36.2 |

^a See Eq. (3).

TABLE IV

The difference between the ^{15}N substituent chemical shifts of ureas and thioureas^a after acylation to the second degree (Scheme 1, equation (B))

| R ¹ | R ² = CH ₃ | | R ² = C ₆ H ₅ | |
|-------------------------------|----------------------------------|------|--|------|
| | N-1 | N-3 | N-1 | N-3 |
| CH ₃ | -6.7 | 18.4 | -7.4 | 26.7 |
| C ₆ H ₅ | -5.0 | 17.5 | -6.8 | 17.7 |

^a See Eq. (4).

thioureas VI and VII have non-equivalent $^1J(^{15}\text{N}, \text{H})$ coupling constants at the N-3 nitrogen atom. The higher one of them belongs to the H_α proton which is stabilized by an intramolecular hydrogen bond to the acyl carbonyl group. This proton is in an *s-trans* position to the sulphur atom due to partial double bond character of the $\text{CS}-\text{NH}_2$ bond. This result agrees with the measurements carried out by Roberts¹⁷ who found that $^1J(^{15}\text{N}, \text{H})_{\text{trans}}$ is greater than $^1J(^{15}\text{N}, \text{H})_{\text{cis}}$ for N-alkylformamides. Although 1-(4-nitrophenyl)thiourea is by almost one order of magnitude more acidic¹⁸ than 1-acetylthiourea¹⁹, in its proton-coupled ^{15}N NMR spectrum, its N-3 nitrogen atom gives a triplet with the coupling constant $^1J(^{15}\text{N}, \text{H}) = 90.3$ Hz. Therefrom it follows that the substituent effect on the acidity of the NH protons of thioureas need not correspond to the effect on the non-equivalence of the $^1J(^{15}\text{N}, \text{H})$ coupling constants at N-3 nitrogen atom.

The measurements of ^1H , ^{13}C , and especially ^{15}N NMR spectra and of $^1J(^{15}\text{N}, \text{H})$ coupling constants enabled a detailed description of acylated and diacylated ureas and thioureas as well as unambiguous estimation of the position of the acylation to the second degree.

REFERENCES

1. Hegershoff A.: Chem. Ber. 58, 2477 (1925).
2. Douglas I. B., Dains F. B.: J. Am. Chem. Soc. 56, 719 (1934).
3. Werner E. A.: J. Chem. Soc. 109, 1120 (1916).
4. Dixon A. E., Hawthorne J.: J. Chem. Soc. 91, 139 (1907).
5. Bax A.: J. Magn. Reson. 57, 314 (1984).
6. Jirman J.: Czech. 245 088 (1986).
7. Speziale A. B., Smith L. R.: Org. Synth., Coll. Vol. V, 204 (1955).
8. Micich T. J.: J. Am. Oil. Chem. Soc. 59, 92 (1982); Chem. Abstr. 96, 217 411 (1982).
9. Anschütz R., Montfort W. F.: Liebigs Ann. Chem. 284, 1 (1895).
10. Kaválek J., Jirman J., Štěrbá V.: Collect. Czech. Chem. Commun. 52, 120 (1987).
11. Billeter O. C.: Chem. Ber. 36, 3217 (1903).
12. Stoughton R. W.: J. Org. Chem. 2, 519 (1938).
13. Jirman J., Kaválek J., Macháček V.: Sb. Ved. Pr., Vys. Sk. Chemickotechnol., Pardubice, in press.
14. Buděšínský M., Samek Z., Tichý M.: Collect. Czech. Chem. Commun. 45, 2784 (1984).
15. Martin G. J., Martin M. L., Gouesnard J. P. in the book: ^{15}N NMR Spectroscopy (P. Diehl, E. Fluck and R. Kosfeld, Eds), p. 136. Springer, Berlin 1981.
16. Kaválek J., Said El Bahaie, Štěrbá V.: Collect. Czech. Chem. Commun. 49, 2103 (1984).
17. Nakanishi H., Roberts J. D.: Org. Magn. Reson. 15, 7 (1981).
18. Kaválek J., Štěrbá V., Said El Bahaie: Collect. Czech. Chem. Commun. 48, 1430 (1983).
19. Kaválek J., Jirman J., Macháček V., Štěrbá V.: Collect. Czech. Chem. Commun. 52, 1992 (1987).

Translated by J. Panchartek.