Tetrahedron. Vol. 32, pp 2127 to 2129 Pergamon Press 1976. Printed in Great Britain

A ^{14}N NMR STUDY OF THE ISOMERIC STRUCTURES OF UREA AND ITS ANALOGUES

M. WITANOWSKI, L. STEFANIAK, S. SZYMAŃSKI
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

and

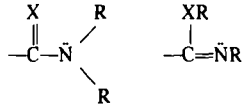
G. A. WEBB*
Department of Chemical Physics, University of Surrey, Guildford, Surrey, England

(*Received in UK* 15 *March* 1976; *Accepted for publication* 29 *March* 1976)

Abstract—In urea and its structural analogues differences in excess of 100 ppm are found in the nitrogen screening constants for the amide- and isoamide-type structures. The nitrogen chemical shifts are interpreted within the framework of Pople's gauge dependent atomic orbital approximation using INDO molecular orbitals. It is demonstrated that this method provides reasonable values for nitrogen absolute screening constants. The experimental data reported should be useful in examinations of tautomeric equilibria in amides and related structures.

INTRODUCTION

The isomeric pairs of structures, **A** and **B**, where X represents O, S or NR, contain N atoms in distinctly different electronic environments.



A **B**

Structure **A** corresponds to amides and thioamides, structure **B** to the corresponding isoamides (imino-ethers), and isothioamides (imino-thioethers) and both structures refer to guanidine. In **A** the lone pair electrons may be partially delocalized rendering some double-bond character to the CN bond. However in **B** the lone pair comprises part of the σ-electron system of the molecule and the CN bond may be considered as a true double bond. If either, or both, of the R substituents in **A** and **B** are H then tautomeric equilibria are expected to occur between the corresponding pairs of isomers.

The considerable differences in bonding of the N atoms in **A** and **B** may be reflected in their ^{14}N NMR spectra. Comparable differences have been reported for the pyrrole- and pyridine-type N atoms in conjugated heterocycles.[1] We report here our attempts to verify this proposal and to establish characteristic nitrogen chemical shift ranges for **A** and **B** by measurement of the appropriate N-Me and O-Me derivatives which are incapable of undergoing tautomeric change.

If the nitrogen chemical shift difference between **A** and **B** is large, compared with the effect of introducing Me substituents, then nitrogen NMR could become a convenient tool for the investigation of tautomerism in amides and related structures.

RESULTS AND DISCUSSION

The compounds examined in the present work (Table 1) include derivatives of urea, thiourea, isourea, isothiourea and guanidine. The latter contains both types of N atoms, amide and isoamide, in a 2:1 proportion. The data given in Table 1 indicate that the chemical shifts of the amide-type N atoms are only slightly affected by the isomerisation of derivatives of urea and thiourea into the iso-form. However, the difference between the amide-type and the isoamide-type N atoms is as large as 120–180 ppm with the former being more highly screened.

It may be interesting to compare the averaged chemical shifts for the isourea and isothiourea systems with those for urea and thiourea, respectively. The differences, about 40 ppm for the former and about 90 ppm for the latter case, may be used as rough estimates in forming qualitative conclusions concerning the tautomeric equilibria. They suggest that (up to 10 mole %) there is little, if any, of the isourea forms in aqueous solutions of urea and its derivatives (compounds I, II, III) whilst an appreciable contribution of the isothiourea system may be expected in the equilibrium in aqueous solutions of thiourea derivatives (compounds VI, VII).

An explanation of the shift between the N signals of the amide and isoamide structures has been sought in terms of approximate theories of nuclear screening in molecules. The average excitation energy (AEE) approach, which has been frequently employed in discussions of nitrogen chemical shifts[1] and gives good results particularly when combined with INDO molecular orbital calculations,[2] may be used only within groups of molecules with similar structures. Since the N nuclei in the molecules considered here are in two appreciably different sets of electronic environments the AEE approach is not suitable in this case.

We have employed the method suggested by Pople[3,4] in which gauge-dependent atomic orbitals are used in the derivation of local diamagnetic and paramagnetic contributions, σ^d and σ^p respectively, to the nuclear screening tensor. Where for atom A,

$$\sigma_A{}^d = \frac{\mu_0}{4\pi}\frac{e^2}{3m}\sum_{\mu} P_{\mu\mu}\langle\mu|r_{\mu A}^{-1}|\mu\rangle \qquad (1)$$

and

$$\sigma_A{}^p = -\frac{\mu_0}{4\pi}\frac{\hbar^2 e^2}{2m^2}\langle r^{-3}\rangle_{2P}\sum_{j}^{occ}\sum_{k}^{unocc}(E_k - E_j)^{-1}$$

Table 1. ^{14}N NMR spectra of some ureas, thioureas and guanidines

Number	Compound	Solvent	Internal standard	^{14}N Chemical shift (ppm) (a)	Signal half-height width (Hz)
I	$H_2N-C(=O)-NH_2$	H_2O	KNO_3	+302.8 ± 0.7	360.1 ± 9.0
II	$MeNH-C(=O)-NH_2$	H_2O	KNO_3	+310.7 ± 1.2	1093.4 ± 24.6
III	$MeNH-C(=O)-NHMe$	H_2O	KNO_3	+297.4 ± 3.1	2803.0 ± 111.7
IV	$Me_2N-C(=O)-NMe_2$	H_2O	KNO_3	+312.5 ± 2.1	2012.0 ± 57.1
		neat	$MeNO_2$	+320.5 ± 0.5	743.0 ± 8.3
V	$Me_2N-C(OMe)=NH$	neat	$MeNO_2$	+319.5 ± 4.1 (NMe_2)	839.3 ± 46.9
				+238.3 ± 0.4 (=NH)	217.0 ± 5.4
VI	$H_2N-C(=S)-NH_2$	H_2O	KNO_3	+269.3 ± 0.4	215.0 ± 4.4
VII	$MeNH-C(=S)-NH_2$	H_2O	KNO_3	+279.2 ± 1.2	450.1 ± 17.6
VIII	$Me_2N-C(=S)-NMe_2$	acetone	$MeNO_2$	+300.5 ± 0.9	670.4 ± 14.8
IX	$Me_2N-C(SMe)=NMe$	neat	$MeNO_2$	+299.6 ± 3.6 (NMe_2)	984.9 ± 37.8
				+120.6 ± 1.0 (=NMe)	423.8 ± 14.1
X	$Me_2N-C(=NH)-NMe_2$	neat	$MeNO_2$	+333.4 ± 1.4 (NMe_2)	884.3 ± 17.9
				+207.8 ± 0.7 (=NH)	315.9 ± 8.3
XI	$Me_2N-C(=NMe)-NMe_2$	neat	$MeNO_2$	+334.0 ± 1.6 (NMe_2)	1164.1 ± 24.8
				+187.0 ± 1.1 (=NMe)	558.4 ± 14.6

(a) Chemical shifts are expressed on the screening constant scale[1]. An increase in screening with respect to CH_3NO_2 corresponds to a positive shift.

$$\times\Big[(C_{j,x_A}C_{k,y_A}-C_{j,y_A}C_{k,x_A})\sum_B(C_{j,x_B}C_{k,y_B}-C_{j,y_B}C_{k,x_B})$$

$$+(C_{j,y_A}C_{k,z_A}-C_{j,z_A}C_{k,y_A})\sum_B(C_{j,y_B}C_{k,z_B}-C_{j,z_B}C_{k,y_B})$$

$$+(C_{j,z_A}C_{k,x_A}-C_{j,x_A}C_{k,z_A})\sum_B(C_{j,z_B}C_{k,x_B}-C_{j,x_B}C_{k,z_B})\Big] \quad (2)$$

In eqn (1) $P_{\mu\mu}$ is the charge density in atomic orbital μ at an average distance of $r_{\mu A}$ from nucleus A. In eqn (2) C_j, x_A is the unperturbed LCAO coefficient of the P_x orbital on A in the molecular orbital j, etc. the summation over all nuclei B includes A, E_k and E_j refer to the energies of the molecular orbitals k and j, unoccupied and occupied respectively. The excitation energy, $(E_k - E_j)$ is evaluated from

$$E_k - E_j = \epsilon_k - \epsilon_j - J_{jk} + 2K_{jk} \quad (3)$$

where ϵ_k and ϵ_j are eigenvalues of the unperturbed molecule, J_{jk} and K_{jk} are respectively the Coulomb and exchange integrals. In the present work eqns (1)–(3) have been evaluated by means of INDO molecular orbital data. In eqn (2), $\langle r^{-3}\rangle_{2p}$ refers to the mean inverse cube of the radius for the $2p$ orbitals on A, this is approximated by

$$\langle r^{-3}\rangle_{2p} = \frac{1}{3}\left(\frac{Z_{2p}}{2a_0}\right)^3. \quad (4)$$

Where Z_{2p} is the effective nuclear charge for the $2p$ electrons and a_0 is the Bohr radius. The value of Z_{2p} may be obtained from Slater's rules[5] or by Burn's method.[6] Both approaches have been used in the present work for eqns (1) and (4).

The INDO program used does not contain sulphur parameters hence those molecules containing S were not included in the nuclear screening calculations. The calculated results obtained by using Slater's rules are given in Table 2.

The correlation between the observed and calculated chemical shifts is reasonable for quantitative agreement a sealing factor of about two is necessary. This may be due to the method chosen to evaluate eqn (4) since Burn's method provides a similar correlation with a different scaling factor. In spite of this the calculations give a satisfactory account of the direction and relative magnitudes of the nitrogen chemical shifts.

For the molecules considered in Table 2 the calculated differences in nuclear screening arise almost entirely from changes in σ^p. The variation of σ^d is within 2 ppm, i.e. less than 2% of the observed chemical shift difference between the amide and isoamide-type N nuclei, in agreement with other estimates of σ^d for nuclei other than protons.[7]

It has been reported[8,9] from theoretical and molecular beam investigations on N_2 that the absolute nuclear screening in N_2 is about −100 ppm, i.e. in the direction of deshielding. The difference between the nitrogen screening in liquid N_2 and in the standards (CH_3NO_2 and NO_3^-) used in the present work is expected to be about −70 ppm.[10,11] Thus on the absolute screening scale the standards should appear at about −170 ppm. This value may be in error by up to ±30 ppm since the standards have not been measured accurately relative to gaseous N_2 and the estimate of the absolute value for N_2 may introdube errors.

The final column of Table 2 presents the differences between total calculated nitrogen screening constant and the corresponding experimental nitrogen chemical shift with respect to $MeNO_2$ for a selection of molecules. The

Table 2. Comparison of theoretical and experimental nitrogen chemical shifts for some ureas and guanidines

Compound		^{14}N chemical shift (ppm) $\sigma^{exp}_{CH_3NO_2}$	calculated screening constant (ppm) σ^d	σ^p	σ^{total}	$\sigma^{total} - \sigma^{exp}_{CH_3NO_2}$
XI	(—NMe_2)	+334	+326.7	−188.5	+138.2	−196
IV	(—NMe_2)	+320	+326.7	−184.5	+142.2	−178
V	(—NMe_2)	+320	+326.5	−191.1	+135.4	−185
V	(=NH)	+238	+327.7	−250.6	+77.1	−159
XI	(=NMe)	+187	+328.5	−262.8	+65.7	−121

mean of these differences is about −160 ppm to within ±35 ppm limits. Consequently the use of eqns (1)–(4) together with INDO molecular orbitals and Slater's rules appears to provide reasonable values for the absolute nitrogen screening constants in the molecules considered. This lends further significance to the choice of method for calculating σ^P since the AEE approach tends to produce numerical values which, at best, reflect chemical shift trends in a group of closely related molecules.

In compounds IV and VIII of Table 1, tautomerism is not possible. Thus, the nitrogen chemical shifts of the amide and thioamide structures are very similar. However for the N–R nitrogen nuclei in the isourea and isothiourea structures the chemical shift difference is about 70 ppm. This taken together with any difference in the tautomeric equilibrium constants between amides and thioamides may be responsible for the nitrogen nuclei in the latter being deshielded by about 50 ppm.[1]

EXPERIMENTAL

The ^{14}N NMR spectra were measured at 4.3342 MHz modulated by an audio-frequency of 2 kHz using a Varion HA-60IL Spectrometer in a field-swept CW mode. The measurements were carried out at room (30°C) temperature in 15 mm o.d. sample tubes without spinning. $MeNO_2$ or KNO_3 were used in trial amounts as internal standards. The chemical shifts and line widths were obtained by a least-squares fitting of theoretical spectral curves to experimental spectra. The errors quoted in Table 1 are standard deviations for about 200 data points per spectrum.

The compounds examined were either commercial c.p. grade or were synthesised according to published procedures: V[12], IX[13] and XI.[14]

The INDO calculations were performed on the University of London CDC 7600 Computer using a modified version of QCPE 141. The geometries employed are standard ones.[15]

Acknowledgements—We are indebted to Dr. S. Peksa for the syntheses and to K. A. K. Ebraheem for useful discussions and for assistance in writing the nuclear screening program.

REFERENCES

[1] *Nitrogen NMR* (Edited by M. Witanowski and G. A. Webb) pp. 14–31, 187–196; and Refs therein. Plenum Press, London (1973).
[2] M. Witanowski, L. Stefaniak, H. Janusezweski and G. A. Webb, *J. Mag. Res.* **16**, 69 (1974).
[3] J. A. Pople, *Disc. Faraday Soc.* **34**, 7 (1963).
[4] J. A. Pople, *J. Chem. Phys.* **37**, 53, 60 (1962).
[5] J. C. Slater, *Phys. Rev.* **36**, 57 (1930).
[6] G. Burns, *J. Chem. Phys.* **41**, 1521 (1960).
[7] K. A. K. Ebraheem, G. A. Webb and M. Witanowski, *Org. Mag. Res.* in press (1976).
[8] M. R. Baker and N. F. Ramsey, *Phys. Rev.* **133A**, 1533 (1964).
[9] S. I. Chan, M. R. Baker and N. F. Ramsey, *Ibid.* **136A**, 1224 (1964).
[10] J. E. Kent and E. L. Wagner, *J. Chem. Phys.* **44**, 3530 (1966).
[11] C. H. Bradley, G. E. Hawkes, E. W. Randall and J. D. Roberts, *J. Am. Chem. Soc.* **97**, 1958 (1975).
[12] F. H. S. Curd, D. G. Davey and D. N. Richards, *J. Chem. Soc.* 1732 (1949).
[13] H. Lecher and F. Graf, *Ber. Dtsch. Chem Ges* **56**, 1328 (1923).
[14] H. Z. Lecher, E. M. Hardy and C. L. Kosloski, *U.S. Pat.* 2,845,459 (1958).
[15] J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967).