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MOLECULAR CONFORMATION OF 1,3-PYRIDYLPHENYLUREAS BY ^{1}H AND ^{13}C NMR STUDY

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ABSTRACT

^{1}H and ^{13}C NMR spectra are reported for several 1,3-pyridylphenyl ureas. Analysis of the spectra yielded the chemical shifts. The variations in the chemical shifts have been discussed in terms of the molecular conformations.

INTRODUCTION

Several studies have been reported concerning the relative conformer stability of urea derivatives, mainly alkylated ureas; there have been few reports on the molecular conformation of arylurea derivatives [1—4]. For 1,3-disubstituted ureas, four planar conformers stabilized by extensive delocalization can be written (Fig. 1). The *E,Z* and *Z,E* rotamers are equivalent for identical substituents. The *E,E* rotamer is generally excluded on steric grounds. The preferred conformation for 1,3-dialkylureas, with less bulkier alkyl groups is the *Z,Z*-type [3, 4]. Galabov and co-workers [5, 6] studied the conformational isomerism of some 1,3-diphenyl thiourea derivatives chiefly by infrared spectroscopy. It was inferred that at room temperature and in organic solvents the compounds participate in a "complex equilibrium" between several forms. We considered it interesting to study the ^{1}H and ^{13}C NMR spectra of some 1,3-pyridylphenylurea systems, which have biological relevance [7—9]. Further, partially substituted ureas could be relevant models in understanding the steric rigidity of polypeptides and proteins [10, 11].

EXPERIMENTAL

The compounds were prepared by the following procedure. Phenyl isocyanate (1 M) and the appropriate heterocyclic amine (1 M) were taken in dry dioxane and kept at room temperature for 24 h. The crystals which separated were collected and washed with ice cold dioxane. The compounds were spectroscopically pure. The compounds included in the study are RNHCONHph(ph = phenyl) where:

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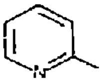
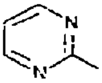
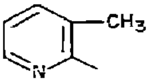
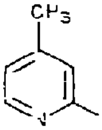
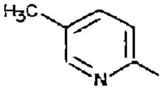
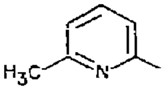
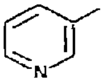
Compound	R	M.p. (°C)
(1)		192—194
(2)		233—235
(3)		178—180
(4)		182—184
(5)		198—200
(6)		196—200
(7)		230—232

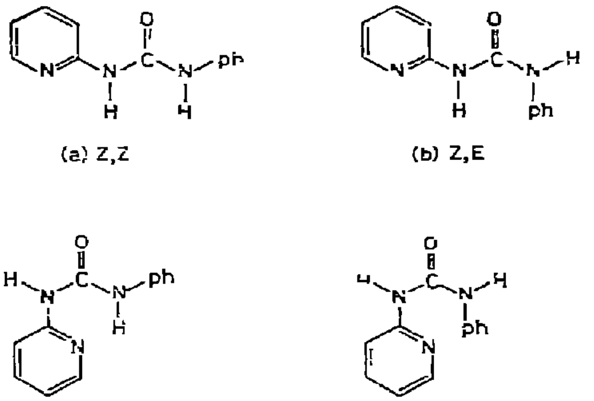

(a) Z,Z
(b) Z,E
(c) E,Z
(d) E,E

Fig 1 Four configurational isomers of 1,3-pyridylphenylureas.

^{1}H NMR spectra were recorded at 270 MHz on a Bruker WH 270 Fourier Transform spectrometer, to which is attached a computer with 20 K memory. Solutions were made in $CDCl_3$ or DMSO-d_6 containing 1% TMS as internal standard. Experimental parameters used were: spectral width 4000 Hz, pulse width 5 μs, acquisition time 3.0 s and number of pulses 20—30.

^{13}C NMR spectra were recorded on the same instrument operating at 67.89 MHz. Broad-band decoupled spectra were recorded in the usual way. Experimental parameters employed were: spectral width 17 240 Hz, pulse width 15 μs, acquisition time 3.0 s and number of pulses 100—400. ^{13}C single frequency FT spectra were recorded adopting the gated decoupling technique. The experimental parameters were spectral width 6042 Hz, pulse width 15 μs, acquisition time 3 5 s and number of pulses 6000—11 000. The chemical shifts were measured relative to TMS used as an internal standard

RESULTS AND DISCUSSION

The chemical shifts for the N—H, aryl and alkyl protons at ambient temperature in $CDCl_3$ are listed in Table 1 The spectrum of a representative compound (6) is shown in Fig. 2. The spectrum of (7) shows a single signal at 8.67 ppm, in contrast to all the other compounds which display two signals, one near 8.5—10.0 ppm and the other in the region ~12 0 ppm. The existence of the latter extreme low-field signal suggests the presence of strong intramolecular hydrogen bonding [12, 13] Inspection of the rotamers in Fig. 1 shows that the *E,Z* isomer of the 1,3-pyridylphenylureas possesses suitable geometry for the formation of strong internal N—H···N (2-pyridine) hydrogen bonding. The extreme downfield signal can then be attributed to the N—H group in the *E* configuration and the other signal in the region 8.0—10.0 ppm to the N—H group in the *Z*-configuration of the —NHCONH— group of the *E,Z* isomer. It is known that 1,3-disubstituted ureas can form intermolecular N—H···O hydrogen bonds [14]. The upfield shift of the N—H in the *Z*-configuration (NH_Z) for (3) and (6) could be interpreted as due to steric influence of the methyl groups preventing intermolecular hydrogen bonding.

The *E,Z* rotamer for 1,3-pyridylphenyl ureas is apparently stabilized by the intramolecular hydrogen bonding. Further support in favour of this structure comes from the values of the chemical shifts of the pyridyl protons listed in Table 1. Thus, the large upfield shift of the H-3 proton of the pyridyl group is noted while the chemical shifts of the other protons are comparable with the corresponding ones in simple 2-substituted pyridines [15]

Owing to the poor solubility of compounds (2) and (7), their ^{13}C NMR spectra could not be obtained The remaining compounds were appreciably soluble in DMSO-d_6 and their ^{13}C spectra were recorded The ^{13}C chemical shifts are also assembled in Table 1. The assignments of the individual carbon resonances are based on the signal pattern obtained with complete proton

TABLE 1

Observed ^{1}H and ^{13}C chemical shifts (δ, ppm)

(i) ^{1}H Chemical shifts

Compound	Pyridyl					–CH$_3$	N–H (*E*)	N–H (*Z*)
	H–2	H–3	H–4	H–5	H–6			
(1)	–	7.02	7.76	7.07	8.30	–	12.57	9.50
(2)	–	–	7.30	6.85	–	–	11.49	10.20
(3)	–	–	7.52	6.94	8.15	2.28	12.18	8.12
(4)	–	6.95	–	7.08	8.20	2.30	12.69	9.41
(5)	–	6.92	7.42	–	7.98	2.23	12.50	9.30
(6)	–	6.72	7.58	6.92	-	2.48	12.26	8.44
(7)	8.53	–	7.34	7.85	8.28	–	8.67	

(ii) ^{13}C Chemical shifts

Compound	Pyridyl						Phenyl			
	C=O	C–2	C–3	C–4	C–5	C–6	C–o	C–m	C–p	C–q
(1)	162.12	153.52	112.52	138.72	118.27	144.22	125.12	126.12	128.75	139.12
(3)	161.75	151.72	110.42	139.89	119.21	142.24	124.80	125.24	128.92	130.32
(4)	161.89	153.58	112.83	150.62	119.73	145.20	124.86	126.08	128.94	138.95
(5)	162.35	151.09	111.82	139.62	127.42	145.30	124.50	126.22	128.42	138.98
(6)	161.92	152.92	109.47	139.21	117.59	155.12	124.22	125.98	128.53	139.02

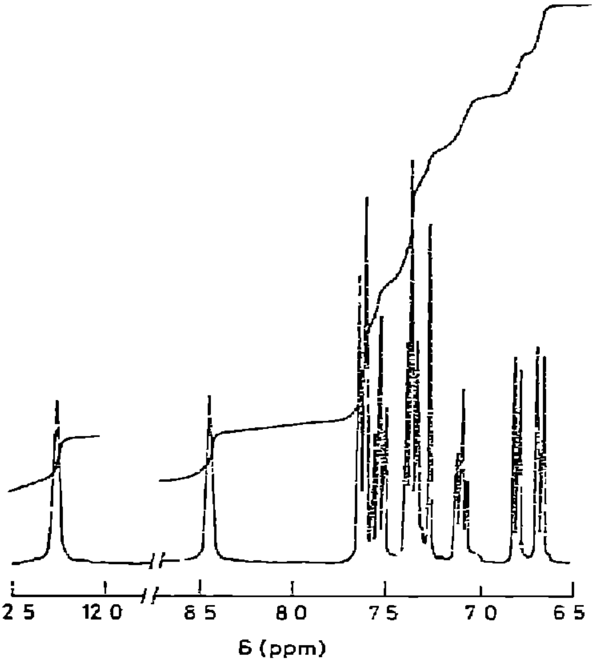


Fig 2. ^1H NMR spectrum of (6) in $CDCl_3$ in the N—H and aromatic regions

decoupling versus those obtained in the proton-decoupled spectra measured using gated decoupling [16, 17] The chemical shifts for the C—2 and C—6 (*ortho* to the heterocyclic nitrogen) for the pyridyl ring are shifted upfield relative to the analogous ones in simple 2-substituted pyridines [18] due to the increased mesomeric interaction of the thioureide nitrogen lone pair with the *E*-pyridyl ring. This arises consequent to the formation of internal N—H···N(py) hydrogen bonding The remaining pyridine carbons show smaller lowfield shifts The ^{13}C chemical shifts of the four magnetically non-equivalent carbon atoms of the phenyl ring were clearly distinguishable from peaks due to the carbons of the pyridine ring in each spectrum on the basis of their intensities and constancy of the values of the chemical shifts in each spectrum [16]. Further, that the carbon atom assigned to the quaternary carbon is not bonded to hydrogen is shown by the off-resonance spectra

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