^{1}H and ^{13}C NMR spectra of some unsymmetric *N*,*N*′-dipyridyl ureas: spectral assignments and molecular conformation

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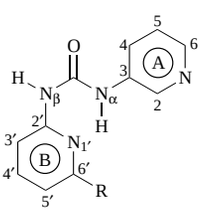
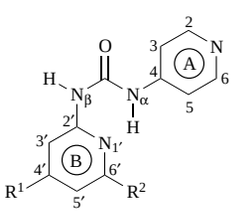
The ^{1}H NMR spectra of *N*-(2-pyridyl), *N*′-(3-pyridyl)ureas and *N*-(2-pyridyl), *N*′-(4-pyridyl)ureas in $CDCl_3$ and $(CD_3)_2CO$ have been assigned with the aid of COSY and NOE experiments and chemical shift and coupling constant correlations. The ^{13}C NMR spectra in $CDCl_3$ were analysed utilizing the HETCOR and proton coupled spectra. The ^{1}H NMR spectra, NOE effects and MINDO/3 calculations have been utilized to show that the molecular conformation of these compounds has the 2-pyridyl ring coplanar with the urea plane with the N–H group hydrogen bonded to the nitrogen of the 2-pyridyl group on the other urea nitrogen while the 3/4-pyridyl group rotates rapidly about the N–C^3/N–C^4 bond.

Different alkyl, aryl and arylalkyl derivatives of urea and thiourea have been investigated by NMR spectroscopy to understand their conformational behaviour as model systems for polypeptides and proteins.[1–10] However, little is known of the molecular conformations of unsymmetrical *N*,*N*-dipyridyl ureas which form an interesting class of aromatic ureas bearing pyridyl groups. These derivatives are also of interest due to their biological importance.[11–12]

A study of the ^{1}H and ^{13}C NMR spectra and molecular conformations of *N*-(2-pyridyl),*N*′-(3-pyridyl)urea and *N*-(2-pyridyl),*N*′-(4-pyridyl)urea and their methyl derivatives (**1**–**5**) in



1: R = H
2: R = Me



3: $R^1 = R^2 = H$
4: R^1 = Me, R^2 = H
5: R^1 = H, R^2 = Me

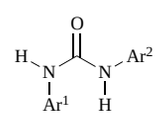
N-(2-pyridyl), *N*′-(3-pyridyl) ureas (**1** and **2**) and (*b*) *N*-(2-pyridyl), *N*′-(4-pyridyl) ureas (**3** to **5**)

$CDCl_3$ and $(CD_3)_2CO$ is discussed in this paper. The ^{1}H NMR spectra were analysed from the correlations in the COSY spectra and the NOE experiments. The ^{1}H chemical shifts and coupling constants have been obtained from simulation of the resolution enhanced spectra. The ^{1}H chemical shifts, NOE experiments and molecular orbital calculations at the MINDO/3 level were utilized to obtain information on molecular conformations. The ^{13}C NMR spectra were analysed with the help of HETCOR and proton coupled ^{13}C spectra and the ^{13}C–^{1}H coupling constants obtained by the simulation of the proton coupled ^{13}C spectra.

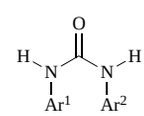
N,*N*′-Diarylureas ($Ar^1NHCONHAr^2$) can theoretically exist in four planar conformations[7,8] shown in Fig. 1. Increased electron delocalization over the urea moiety favours a planar structure. When the aryl groups are not coplanar with the ureide plane, the number of possible conformations is theoretically higher. Molecular conformational studies of a number of pyridyl and pyridylphenyl derivatives of urea and thiourea from ^{1}H and ^{13}C NMR spectra have been carried out in our laboratory.[5–9] These studies have demonstrated that the symmetric *N*,*N*′-dipyridyl thioureas exist either in the *ZE* or the *EZ* conformation (Fig. 1) at low temperature (below 233 K), while at ambient temperature they exist in an equilibrium mixture of *ZE* and *EZ* forms. On the other hand, unsymmetrical *N*,*N*′-dipyridyl and *N*-pyridyl-*N*′-phenyl ureas and thioureas when one of the groups is 2-pyridyl have been found to be present in the *EZ* form.

ZZ (*trans* – *trans*)

ZE (*trans* – *cis*)



EZ (*cis* – *trans*)



EE (*cis* – *cis*)

Fig. 1 Planar conformations of *N*,*N*′-disubstituted ureas

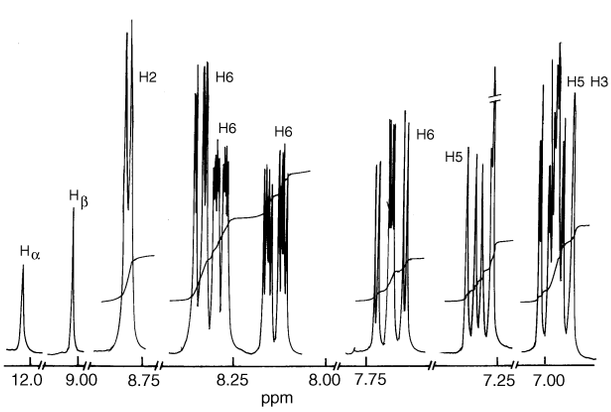


Fig. 2 ^{1}H NMR spectrum of **1** in $CDCl_3$ on 200 MHz spectrometer

Results and discussion

Assignment of ^{1}H NMR spectra

The ^{1}H NMR of **1** and COSY spectra of **2** are shown in Figs. 2 and 3 respectively as representative spectra. The ^{1}H chemical shift assignments for **1**–**5** in different solvents as verified by COSY experiments are presented in Table 1. The simulated

Table 1 ^{1}H Chemical shifts[a] (δ) of **1**–**5**

Compound	Solvent		H2	H3,H3′	H4,H4′	H5,H5′	H6,H6′	NH_α	NH_β
1	$CDCl_3$	3-Py	8.79		8.14	7.30	8.34	12.16	9.29
		2-Py		6.95	7.69	6.98	8.28		
N2PA[c]		2-Py		8.29	7.72	7.05	8.29	10.39	
	$(CD_3)_2CO$	3-Py	8.83		8.21		8.30	11.71	8.95
		2-Py			7.85	7.11	8.42		
2	$CDCl_3$	3-Py	8.73		8.19	7.30	8.33	12.58	8.61
		2-Py		6.67	7.57	6.83			
	$(CD_3)_2CO$	3-Py	8.80		8.21	7.37	8.30	12.10	8.92
		2-Py		7.10	7.73	6.98			
N3PA[c]	$CDCl_3$	3-Py	8.57	—	8.18	7.26	8.30	—	8.58
	$(CD_3)_2CO$		8.80	—	8.21	7.36	8.33	—	9.47
3	$CDCl_3$	4-Py	8.51	7.58		7.58	8.51	12.34	9.31
		2-Py		6.95	7.32	7.01	8.29		
N4PA[c]		4-Py	8.50	7.48		7.48	8.50		7.74
	$CDCl_3$[b]	4-Py	8.45	7.59		7.59	8.45	12.01	8.92
	$(CD_3)_2CO$	2-Py		7.20	7.72	7.02	8.31		
4	$(CD_3)_2CO$	4-Py	8.41	7.60		7.60	8.41	11.97	8.84
		2-Py		7.11		6.93	8.22		
5	$CDCl_3$	4-Py	8.50	7.54		7.54	8.50	12.73	8.40
		2-Py		6.66	7.59	6.86			
	$(CD_3)_2CO$	4-Py	8.42	7.59		7.59	8.42	12.17	8.90
		2-Py		7.06	7.69	6.94			

[a] Numbering follows from Fig. 1. [b] 1:1 mixture of the solvents. [c] N2PA, N3PA and N4PA denotes *N*-(2-pyridyl)acetamide (ref. 13) *N*-(3-pyridyl)acetamide (ref. 14) and *N*-(4-pyridyl)acetamide respectively (ref. 14).

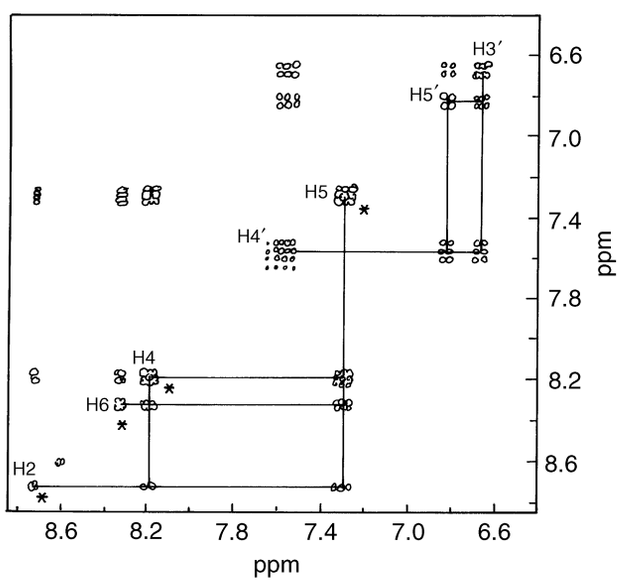


Fig. 3 COSY spectrum (contour plot) of **2** in $CDCl_3$ on 200 MHz spectrometer

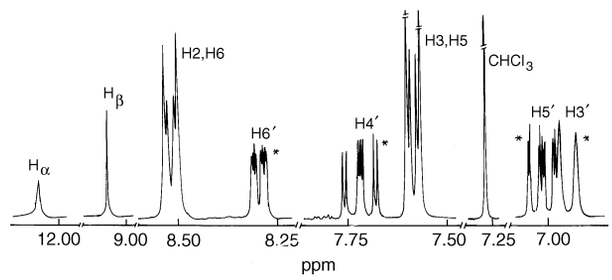


Fig. 4 Resolution enhanced ^{1}H NMR spectrum of **3** in $CDCl_3$

spectra were also in good agreement with the experimental spectra. For example, the ^{1}H NMR spectrum of **1** in $CDCl_3$ which is not a pure first-order spectrum was simulated in good agreement with the experimental spectrum (RMS error for the protons of the rings A and B were 0.063 and 0.065 ppm respectively). The two singlets at 9.29 and 12.16 ppm in the spectrum of **1** arise respectively from H_β and H_α protons and they occur in **2**–**4** in the same region. They were assigned on the basis of the NOE enhancements. Irradiation of the signal at 12.16 ppm gave NOE enhancement at H2 (4.3%) and H4 (2.5%) as well as at H6′. On the other hand, irradiation of the signal at 9.29 ppm showed NOE only at H3′. The chemical shift assignments for the 2-pyridyl group except H3′ are consistent with those made very recently for *N*-(2-pyridyl)acetamide (N2PA) and *N*(2-pyridyl)benzamide (N2PB) which have a similar planar *trans* Py–NH–CO– structure.[13] The chemical shifts for N2PA and N2PB are included in Table 1 for comparison. On this basis, a shift of *ca*. 1.6 ppm may be expected due to hydrogen bonding, a shift of *ca*. 1 ppm from strong deshielding due to the ring current neglecting the inductive effect of the other urea nitrogen.

The appearance of H3′ of the 2-pyridyl group (6.7–7.1 ppm) in compounds **1** to **5** is similar to that of 2-aminopyridine (6.49 ppm) suggesting that H3′ does not lie in the anisotropic deshielding zone of the carbonyl group.[13] If the 2-pyridyl ring were to lie in the anisotropic deshielding zone of the C=O group as in N2PA, then the δ value of H3′ would be expected near 8.4 ppm (see Table 1). Thus the *trans* orientation of the 2-pyridyl group with respect to the C=O group as shown in structures **1**–**5** seems justified. The orientation of the 2-pyridyl group of **1**–**5** with respect to the urea plane is also consistent with that reported for *N*,*N*′-dipyridyl and *N*-pyridyl-*N*′-phenyl derivatives of urea and thiourea.[5–9] The ^{1}H chemical shifts of the 3-pyridyl groups of **1** and **2** compare very well with those of *N*-(3-pyridyl)acetamide as shown in Table 1.

The COSY spectrum of **3** showed that the protons of the 4-pyridyl group corresponding to the two diagonal peaks at 7.58 and 8.51 ppm are coupled to each other. Irradiation of the singlet at 12.34 ppm gave NOE enhancement for the doublet at 7.58 ppm. The 12.34 and 7.58 ppm signals were therefore assigned respectively to H_α and the chemically equivalent H3 and H5. The singlet at 9.31 ppm and the doublet at 8.51 ppm were assigned respectively to H_β and the equivalent H2, H6. The spectra of **4** and **5** were similarly assigned. The H3′ shows significant high frequency shift in $(CD_3)_2CO$ compared to that in $CDCl_3$. Correspondingly, H_α shifts to low frequency and H_β shifts to high frequency. This is in accordance with acetone forming intermolecular hydrogen bonding at the expense of intramolecular hydrogen bonding. As a result, a small amount

Table 2 ^{1}H Coupling constants[a] (in Hz) of **1**–**5**

Compound	Solvent		$^4J_{24}/^3J_{3'4'}$	$^5J_{25}/^4J_{3'5'}$	$^4J_{26}/^5J_{3'6'}$	$^3J_{45}/^3J_{4'5'}$	$^4J_{46}/^4J_{4'6'}$	$^3J_{56}/^3J_{5'6'}$
1	$CDCl_3$	3-Py	2.59	0.00	0.00	8.41	1.47	4.74
		2-Py	8.29	0.99	0.81	7.33	1.91	5.11
	$(CD_3)_2CO$	3-Py	2.61	0.00	0.00	8.28	1.47	4.65
		2-Py	8.37	0.99	0.82	7.29	1.90	5.11
2	$CDCl_3$	3-Py	2.65	0.00	0.00	8.30	1.44	4.74
		2-Py	8.13	0.00		7.41		
	$(CD_3)_2CO$	3-Py	2.38	0.00	0.00	8.26	1.36	4.62
		2-Py	8.17	0.00		7.44		
3	$CDCl_3$	2-Py	8.30	0.98	0.82	7.36	1.87	5.15
	$CDCl_3$[b]	2-Py	8.42	0.96	0.77	7.33	1.93	5.13
	$(CD_3)_2CO$							
4	$(CD_3)_2CO$							5.20
5	$CDCl_3$	2-Py	8.14	0.00		7.58		
	$(CD_3)_2CO$	2-Py	8.09	0.00		7.48		

[a,b] As in Table 1.

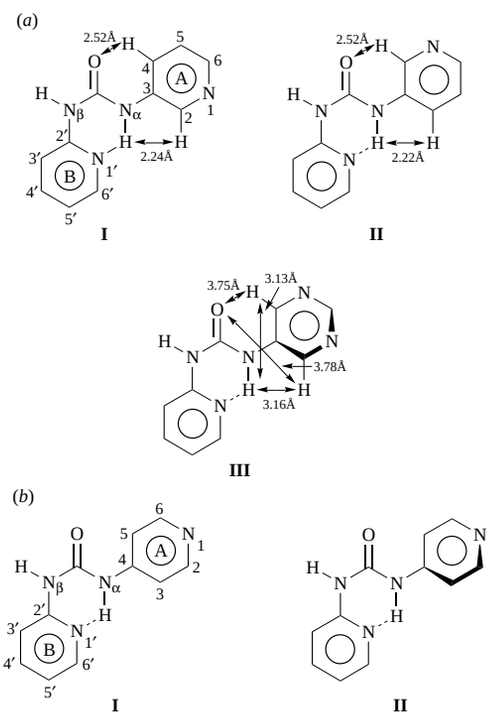


Fig. 5 Possible conformations of (*a*) **1** and (*b*) **3**

of the conformation in which the C=O group is closer to H3′ gives rise to the shift to higher frequency. The NMR spectra of the 4-pyridyls of **3**–**5** are deceptively simple as shown by the RE spectrum of **3** given in Fig. 4 and hence coupling constants could not be obtained. The ^{1}H coupling constants of **1**–**5** in two solvents are presented in Table 2. The coupling constants of the 2-pyridyl group in $CDCl_3$ are nearly the same for **1**–**5**.

Molecular conformations

The ^{1}H NMR spectra were measured in dilute solutions of $CDCl_3$ and $(CD_3)_2CO$ (2–3 mg ml^{-1}) and hence intermolecular association could be excluded.[15] In dilute $CDCl_3$ solution, as discussed before, the δ value of H_α reveals the existence of intramolecular hydrogen bonding between H_α and the 2-pyridyl nitrogen. The 3-pyridyl nitrogen is however geometrically unfavourable for intramolecular hydrogen bonding.

In these compounds, the lone pair on the urea nitrogen is conjugated to the pyridine ring and because of intramolecular hydrogen bonding between H_α and the 2-pyridyl nitrogen, it is expected that the 2-pyridyl ring will be closely coplanar with the ureide group.[13,16] Three possible conformations of **1** where the 3-pyridyl group is orientated differently are shown in Fig. 5. The conformers **I** and **II** are planar, while the 3-pyridyl ring is rotated from the plane of the amide and 2-pyridyl ring by 90° in conformer **III**. Molecular geometry optimizations by the MINDO/3 method were carried out for all three conformers. The conformation **III** (total energy −2622.997 eV) was found to be lower in energy than **I** and **II** by 7.2 and 5.1 kJ mol^{-1} respectively. The calculations are most appropriate in the gas phase analysis but in a polar solution-like environment, the differences are smaller.[17] All the structures are therefore equally probable. However, the ^{1}H NMR spectra of **1**–**5** show that only one conformation is likely to be present on the NMR timescale indicating the rotation of 3-pyridyl in compounds **1** and **2** and, of 4-pyridyl ring in compounds **3**–**5** over the N_α–C3 and N_α–C4 bonds respectively. This is in agreement with the chemical shift equivalence of H2, H6 and H3, H5 of compounds **3**–**5**. Since H3 and H5 of the 4-pyridyl group are chemically equivalent (see Table 1), the 4-pyridyl ring of **3**–**5** cannot be coplanar with the urea plane. If the 4-pyridyl ring were H3 (or H5) should show high frequency shift relative to H5 (or H3), due to the magnetic anisotropic effects of −NHCONH− moiety. The NOE experiment when H_α is saturated is not useful for determining the orientation of the 4-pyridyl ring since H3 and H5 are chemically equivalent. Thus, it is likely the 4-pyridyl group undergoes rapid rotation about the N_α–C4 bond. The same argument holds good for ^{13}C chemical shifts discussed later.

Saturation of H_α of **1** in $CDCl_3$ gave respectively 4.3 and 2.5% NOE enhancements at H2 [$f_2(H_\alpha)$] and H4 [$f_4(H_\alpha)$] respectively. To use the method described by Bell and Saunders[18,19] to obtain the information on distances, it is necessary that dipolar relaxation is the most important relaxation process. In the case of compound **1**, the aromatic protons will also relax by the spin rotation because of the rapid rotation about the N_α–C3 bond. Therefore NOE data were not utilized to obtain distance information.

The ^{1}H chemical shifts of the 3-pyridyl group of **1** are nearly the same in $CDCl_3$ and $(CD_3)_2CO$ (Table 1) and it is therefore likely that the orientation of the 3-pyridyl ring of **1** in these two solvents is similar. The conformation of the 2-pyridyl and the urea moiety for **2**–**5** was found to be the same as that of **1** in $CDCl_3$ as inferred from the ^{1}H chemical shifts of the 2-pyridyl ring (Table 1). The conformation of the 3/4-pyridyl ring about the N_α–C3/N_α–C4 bond is likely to be determined by electron delocalization, dipolar and steric interactions.

Intramolecular hydrogen bonding between H_α and the nitrogen of the 2-pyridyl group and electron delocalization favours coplanarity of the 2-pyridyl ring with the urea moiety. For all three conformations, the calculated bond lengths C2′–N_β, N_β–C, C–N_α and N_α–C3/C4 are nearly the same (1.38 Å), they are shorter than the C–N single bond length (1.47 Å) and the calculated π-bond orders lie in the range 0.35–0.50. The

Table 3 ^{13}C Chemical shifts[a] (δ) of **1**–**5**

Compound	Solvent		C2,C2′	C3,C3′	C4,C4′	C5,C5′	C6,C6′	C=O	C.C.
1	$CDCl_3$	3-Py	141.87	135.48	127.22	123.67	144.47	153.92	0.98
N3PA[c]		3-Py	144.1	135.97	126.32	123.63	140.88	169.23	
		q_T	3.906	3.917	3.974	4.043	3.879	3.312	
		2-Py	152.75	112.34	138.96	117.63	145.95		
		q_T	3.705	4.150	3.883	4.124	3.810		
	$(CD_3)_2CO$	3-Py	144.12	137.14	126.88	125.42	144.76	154.24	
		2-Py	153.51	113.04	139.89	118.43	147.31		
	$CDCl_3$[b]	3-Py	144.10	137.11	126.86	125.40	144.74	154.22	
	$(CD_3)_2CO$	2-Py	153.49	113.02	139.87	118.41	147.29		
N2PA[c]	$CDCl_3$	2-Py	151.8	114.4	138.1	119.1	146.9	169.0	
2	$CDCl_3$	3-Py	144.21	135.75	126.68	123.74	144.29	155.24	0.97
		q_T	3.947	3.902	4.013	4.026	3.909	3.315	
		2-Py	152.06	108.94	139.22	116.86	153.75		
		q_T	3.705	4.152	3.881	4.136	3.808		
3	$CDCl_3$	4-Py	150.43	114.10	150.43	114.10	150.43	153.78	0.98
N4PA[c]		4-Py	150.23	113.37	150.23	113.37	146.01	169.92	
		q_T	3.845	4.110	3.876	4.110	3.846	3.306	
		2-Py	152.61	112.54	139.08	117.90	145.92		
		q_T	3.706	4.149	3.883	4.124	3.811		
4	$CDCl_3$	4-Py	150.41	114.05	150.65	114.05	150.41	153.44	0.97
		q_T	3.845	4.109	3.785	4.109	3.846	3.307	
		2-Py	152.48	112.48	145.97	119.40	145.60		
		q_T	3.705	4.160	3.882	4.134	3.807		
5	$CDCl_3$	4-Py	152.82	116.19	148.38	116.19	152.82	155.75	0.96
		q_T	3.845	4.110	3.785	4.110	3.845	3.306	
		2-Py	154.18	111.41	141.73	119.53	157.59		
		q_T	3.704	4.152	3.881	4.136	3.808		

[a] As in Table 1, C.C. is correlation coefficient, q_T is total electron density. [b,c] As in Table 1.

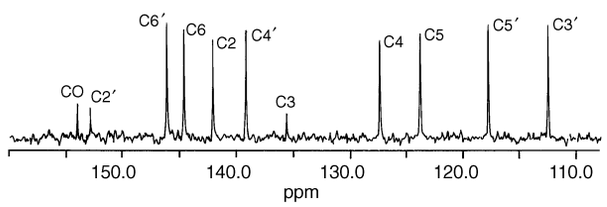


Fig. 6 ^{13}C–{^{1}H} NMR spectrum of **1** in $CDCl_3$

π-bond order of the N_α–C3 bond of **1** decreases from 0.29 to 0.16 when the 3-pyridyl ring is rotated perpendicular to the urea plane. Electron delocalization therefore apparently favours the planarity of the 3/4-pyridyl ring with the urea plane.

^{13}C NMR spectra

The ^{13}C NMR spectra were recorded in dilute solutions of $CDCl_3$ (2–3 mg ml^{-1}). The ^{13}C spectra of **1** were also recorded in $(CD_3)_2CO$ and in a 1:1 mixture of $CDCl_3$ and $(CD_3)_2CO$. Due to the poor solubility of compounds **1**–**5** in $CDCl_3$ and $(CD_2)_2CO$, the proton coupled ^{13}C spectra were recorded only for **1** and **3**.

The ^{13}C and HETCOR spectra of **1** in $CDCl_3$ are shown in Figs. 6 and 7, respectively. The ^{13}C chemical shift assignments for **1** to **5** as verified by HETCOR and proton coupled spectra are presented in Table 3. The assignments for the 2-pyridyl and C=O carbons are consistent with those made very recently for N2PA and N2PB by Katritzky and Ghiviriga.[13] The assignments for 3-pyridyl and 4-pyridyl carbons are in agreement with those made for pyridinecarboxamides from our laboratory.[20] The ^{13}C chemical shifts have been found to correlate linearly with the total electron densities at the relevant carbon atoms for a number of amide, urea and other benzene derivatives.[21–25] The total electron densities at the carbon atoms of **1**–**5** are listed in Table 3. The optimized molecular geometries of II of **1** and **3** (Fig. 5) were used for the electron density calculations. A good linear correlation between ^{13}C chemical shifts and the total electron densities at the carbon atoms were obtained for all (correlation coefficient 0.98) as well as for each of **1**–**5** only when the carbonyl carbon atom was excluded from the data (Table 3).

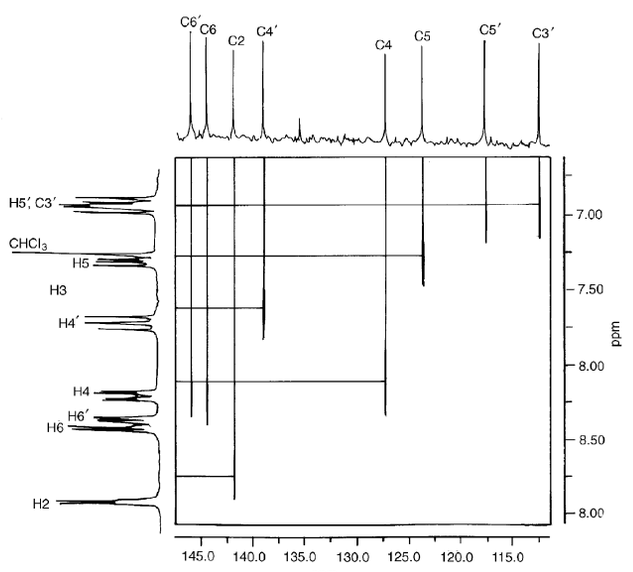


Fig. 7 HETCOR spectrum (contour plot) of **1** in $CDCl_3$

Since the ^{13}C chemical shifts of **1** in different solvents are nearly the same, the conformation is likely to be the same in different solvents consistent with the ^{1}H NMR studies. Comparison of the δ values for C3 (*ca.* 114 ppm) of the 2-pyridyl ring in compounds **1**–**5** with those of 2-aminopyridine (108.5 ppm) suggests that the lone pair on the amino nitrogen is conjugated with the pyridine ring.

The ^{13}C–^{1}H coupling constants of **1** and **3** are given in Table 4. For the carbon atoms which do not give a pure first-order spectrum when recorded on a 200 MHz instrument (the ^{13}C resonates at 50.32 MHz), the ^{13}C–^{1}H coupling constants were obtained by the simulation of the appropriate portion of the proton coupled ^{13}C NMR spectrum.

For the simulation of a portion of the proton coupled ^{13}C spectrum of **3** for C2 and C3, the ^{1}H coupling constants of pyridine[25–27] were used considering the spin systems AA′-

Table 4 $^{13}C–^{1}H$ Coupling constants[a] (in Hz) of **1** and **3** in $(CD_3)_2CO$

Carbon atom	Compound	*J*C,H2	*J*C,H3/ *J*C,H3′	*J*C,H4/ *J*C,H4′	*J*C,H5/ *J*C,H5′	*J*C,H6/ *J*C,H6′
C2	1	180.31		4.40	0.00	11.25
	3	177.84	8.50		2.00	11.82
C5	1	0.00		0.00	162.73	9.50
	3	0.00	8.45		165.15	4.20
C6	1	11.19		7.10	3.05	179.29
	3	177.84	8.50		2.00	11.82
C3′	1		165.66	2.00	6.74	0.00
	3		164.78	0.00	6.43	0.00
C5′	1		6.99	0.00	166.34	6.89
	3		7.00	0.00	166.45	6.80
C6′	1		0.00	7.39	3.99	179.80
	3		0.00	7.24	3.85	179.53

[a] As in Table 1.

BB′CX and AA′BB′X (X = ^{13}C) respectively. The C3 and C5 were found to couple to H_α from the simulation of the spectrum. The three-bond coupling constants between H_α and C3 and C5 are equal (4.4 Hz). It indicates that for **3**, the 4-pyridyl ring is apparently not coplanar with the urea group and undergoes rapid rotation as inferred from the ^{1}H NMR spectrum. The $^{13}C–^{1}H$ coupling constants of **3** are similar to those of **1** and they are also comparable with those of pyridine and its derivatives.[25–27]

Experimental

Synthesis

Unsymmetrical *N*,*N*′-dipyridylureas ($RNHCONHR^1$) are generally prepared by reacting isocyanate (R^1NCO) with an amine (RNH_2) under dry conditions.[28] Isocyanates are synthesized by treating an amine with carbonyl chloride (phosgene) which is highly poisonous and hence advisable to avoid. Isocyanates can also be obtained by heating acid azides (R^1CON_3) which could be obtained by treating the acid chloride (R^1COCl) with NaN_3. However, acid chlorides of pyridine-2- and -3-carboxylic acids are very sensitive to moisture which prevents the formation of acid azides by this method. Therefore, unsymmetrical *N*,*N*′-dipyridylureas were synthesized in the present work by following a five-step procedure.

(*i*) Starting from pyridinecarboxylic acid (Aldrich) its ethyl ester was prepared.[28] (*ii*) The ester was converted into pyridinecarboxylic hydrazide($RCONHNH_2$).[29,30] (*iii*) The acid hydrazide was then converted into acid azide (R^1CON_3).[29,30] (*iv*) The acid azide was converted into isocyanate(R^1NCO) by heating it in dry benzene at 60 °C. (*v*) Finally the isocyanate solution in benzene was reacted with the amine[31] (RNH_2) to obtain *N*,*N*′-dipyridylureas, $RNHCONHR^1$. The products were purified by recrystallization from ethanol. Elemental analyses were in good agreement with the calculated values.

Spectral measurements

^{1}H NMR spectra were recorded at ambient temperature on Bruker AC 270 MHz or Bruker WH 200 MHz FT spectrometers in dilute $CDCl_3$ and $(CD_3)_2CO$ solutions (2–3 mg ml^{-1}). Chemical shifts are given in ppm relative to $SiMe_4$ and the coupling constants in Hz. Steady state 1D NOE experiments were carried out using a 200 MHz instrument on degassed samples in $CDCl_3$ using standard procedures.[18,19] All spectra for NOE studies were acquired with the following parameters: pulse width 5.7 μs, spectral width 3000 Hz, acquisition time 1 s, irradiation time 3–4 s and relaxation delay 5 s. The COSY experiments were performed using the parameters: pulses P_1 and P_2 5.7 μs, spectral width 600–800 Hz, preparation time 1–2 s, number of transients 16 or 32 and the number of experiments 256.

^{13}C NMR spectra were recorded using a Bruker AC (50.32 MHz) or Bruker WH (67.89 MHz) FT spectrometers at ambient temperature. Proton-decoupled and proton-coupled spectra were recorded. Typical conditions were pulse width 90°, spectral width 200–250 ppm, acquisition time 1 s, and relaxation delay 3–5 s. The number of transients were 5000 to 10 000 to obtain a good signal to noise ratio. The HETCOSY spectra with heteronuclear decoupling in both dimensions were recorded on 200 MHz instrument. The experimental parameters used were pulses P_1 to P_4 correspondingly 98, 196, 9.7 and 19.4 μs, spectral width 500 Hz, acquisition time 0.5 s, number of transients 32 or 64 and number of experiments 128 or 256.

The ^{1}H and proton coupled ^{13}C NMR spectra were simulated using the computer program[32] LAOCOON-5. Approximate chemical shifts and coupling constants were obtained from the experimental spectrum. The theoretical spectrum was generated by fitting a Lorentzian line-shape to each of the simulated frequencies. It was plotted on a HP plotter using CALCOMP software. The MO calculations were carried out at the MINDO/3 level using a standard program.[33]

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