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Spectrochimica Acta Part A 53 (1997) 1459–1462

SPECTROCHIMICA ACTA PART A

Short Note

^{1}H and ^{13}C NMR Study of *N*-(3-pyridinyl)-2-pyridinecarboxamide and *N*,*N*′-bis(2-pyridinyl)-1,3-benzenedicarboxamide

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Received 27 September 1996; accepted 21 January 1997

Keywords: NMR spectroscopy; NOE; Conformation; *N*-(3-pyridinyl)-2-pyridinecarboxamide; *N*,*N*′-bis(2-pyridinyl)-1,3-benzene-dicarboxamide

1. Introduction

N-(pyridinyl)carboxamides can theoretically exist in different tautomeric and rotameric structures. In this context and in continuation of our previous studies on pyridinecarboxamides [1,2], a study of conformation by ^{1}H and ^{13}C NMR spectra of *N*-(2-pyridinyl)3-pyridinecarboxamide (**1**) and *N*,*N*′-bis(2-pyridinyl)-1,3-benzenedicarboxamide (**2**) (Fig. 1) is reported.

2. Experimental

Compound (**1**): A mixture of 3-pyridinecarboxylicacid (8.6 g) and 2-pyridylamine (4.7 g) was heated in an oil bath at 180°C for 4 h. The hot reaction mixture was poured with stirring to 200 ml of water. Excess of saturated aqueous solution of $NaHCO_3$ was added to it with stirring and was kept overnight. The product was washed with water, recrystallized from ethanol and dried in air (m.p. 118°, yield 20%).

Compound (**2**): A mixture of 1,3-benzenedicarboxylic acid chloride (2.5 g) containing 1,3-benzenedicarboxylicacid and 2-aminopyridine (3 g) was heated at 180°C for 1 h. It was cooled and treated with excess of saturated aqueous solution of $NaHCO_3$ and was kept overnight. The product obtained was filtered, washed with water and recrystallized from ethanol (m.p. 178°C, yield 15%).

The ^{1}H and ^{13}C NMR spectra were measured on Bruker AC (270 MHz) (^{13}C: 67.89 MHz) spectrometer in $CDCl_3$, CD_3CN and $(CD_3)_2CO$ solutions using Me_4Si as an internal calibrant. Steady state 1D NOE experiments were carried out on degassed samples in $CDCl_3$. The COSY spectra, ^{13}C spectra in coupled and decoupled mode and HETCOSY spectra were all recorded in $CDCl_3$. ^{1}H and proton coupled ^{13}C NMR spectra were simulated using the program LAOCOON-5 [3].

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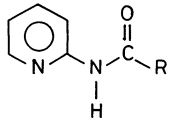
PII S1386-1425(97)00046-2

3. Results and discussion

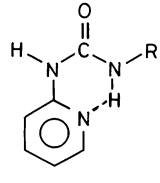
The chemical shift assignments for (**1**) and (**2**) as verified by COSY experiments and literature data for related systems are presented in Table 1 and the COSY spectrum of (**2**) in $CDCl_3$ is shown in Fig. 2. The spectra were also simulated in good agreement with the experimental spectra.

Very recently Katritzky and Ghiviriga [4] utilizing the technique of SIMPLE have shown that *N*-(2-pyridyl)acetamide (2NPA) and *N*-(2-pyridyl)benzamide (2NPB) in $CDCl_3$ and $(CD_3)_2CO$ exist in the following tautomeric-rotamer form



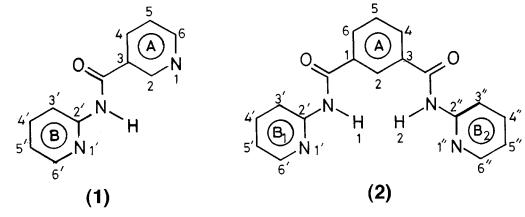
R = CH_3 2NPA
R = C_6H_5 2NPB

In this rotamer, H3 experiences strong deshielding (δ value 8.29 ppm for 2NPA) from the carbonyl group compared with 6.49 ppm in 2- aminopyridine and 7.29 ppm in *N*,*N*-diacetyl-2-aminopyridine [5]. It has been attributed to the coplanar proximity of the carbonyl group. A comparison of the chemical shifts of (**1**) and (**2**) with those of 2NPA and 2NPB shows that for *N*-(2-pyridyl)-CONH- part of (**1**) and (**2**), a planar *trans* structure could be suggested. Although it is possible to conceive other planar conformations for example by 'isolated molecule' MM1 calculations, because of the low energy barrier for rotation over the single bond, the chemical shift of H3′ clearly supports the conformation in which H3′ is closer to the C=O group (see Fig. 1). This was confirmed by the δ value of 7.0 ppm for H3 of *N*-(2-pyridyl), *N*′-(aryl)ureas [1] where the intramolecular hydrogen bonding renders the H3 proton to move away from the C=O group as shown below. However, the 3-pyridyl ring in (**1**) can undergo free rotation about O=C–C3 (pyridyl) bonds because of the low energy barrier and the chemical shifts thus refer to the average values [1].



In concentrated solution, the N–H proton shows high frequency shifts by 1.26 ppm compared with that in dilute solution (Table 1) suggesting intermolecular association through hydrogen bonding. The ring protons experience low frequency shifts in concentrated solution compared to those in dilute solution. In dilute solution (about 1 mg ml^{-1}), NOEs were observed when the NH proton was saturated at H2 (3.3%) and H4 (2.1%), while in the concentrated solution, the NOEs were observed at H3′ (1.0%), H6′ (2.3%) and H6 (0.6%) in addition to that at H2 (6.1%) and H4 (3.3%). To use the method described by Bell and Saunders [6] to obtain information on distances, it is necessary that the important relaxation process should be dipolar. In the case of (**1**), the aromatic protons will also relax by spin rotation because of the rapid rotation about the C–C bond. Hence distance information could not be reliably obtained.

A dimer structure (Fig. 3) may be proposed for the associated species of (**1**) in concentrated solution to account for the concentration dependence of the ^1H NMR spectra and the NOEs. The N–H proton of one molecule is hydrogen bonded to the 2-pyridyl nitrogen of another molecule. The distance of N–H proton from H3′ and H6′ is respectively 3.89 and 4.19 A, while the observed NOE is 1.0 and 2.3% respectively. It suggests that as a result of association, the N–H proton comes closer to H6′ when compared with its distance in the monomer. In the dimer, the N–H proton of one molecule is only 3.03 A away from H6′ of the other molecule. The distances were obtained from molecular modeling of the dimer assuming for simplicity linear intermolecular N–H–N hydro-



(1) (2)

Fig. 1. *N*-(2-pyridinyl)-3-pyridinecarboxamide (**1**). *N*,*N*′-bis(2-pyridinyl)3-pyridinecarboxamide (**2**).

Table 1
^{1}H and ^{13}C Chemical shifts[a] (in δ ppm) of (**1**) and (**2**)

Compound[b]	Solvent	Group[c]	H2, H3′	H4, H4′	H5, H5′	H6′	NH	
(**1**)	$CDCl_3$ (1 mg ml^{-1})	3-py	9.18	8.25	7.47	8.81	8.67	
		2-py	8.38	7.79	7.07	8.31		
	$CDCl_3$ (25 mg ml^{-1})	3-py	9.16	8.21	7.37	8.74	9.86	
		2-py	8.35	7.72	7.00	8.04		
3PCA	$CDCl_3$	3-py	9.03	8.18	7.43	8.76		
2NPA	$CDCl_3$	2-py	8.29	7.72	7.05	8.29	10.39	
2NPB	$CDCl_3$	2-py	8.40	7.64	6.91	7.95	10.38	
(**1**)	$(CD_3)_2CO$	3-py	9.33	8.50	7.62	8.85	9.90	
		2-py	8.42	7.92	7.23	8.41		
	CD_3CN	3-py	9.11	8.26	7.49	8.75	9.24	
		2-py	8.28	7.83	7.15	8.34		
(**2**)	$CDCl_3$	2-py	8.39	7.77	7.08	8.25	9.08	
		ph	8.59	8.16	7.63	8.16		
			CO/C1	C2′	C3′	C4′	C5′	C6′
(**1**)	$CDCl_3$	3-py	164.41	148.67	130.20	135.40	123.58	152.79
3PCA	$CDCl_3$	3-py	170.6	152.5	129.6	137.0	124.9	148.3
		2-py		151.52	114.78	138.78	120.32	147.79
2NPA	$CDCl_3$	2-py	169.0	151.8	114.4	138.1	119.1	146.9
(**2**)	$CDCl_3$	2-py	134.78	151.63	115.06	139.25	120.64	148.26
	$CDCl_3$	ph	134.78	126.54	134.78	131.20	130.04	131.68
2NPB	$CDCl_3$	2-py	166.0	151.6	114.4	138.3	119.4	147.1
Benzamide	$CDCl_3$	ph	134.30	127.40	128.20	131.20	128.20	127.40

[a] Numbering follows from Fig. 1.
[b] 2NPA, 2NPB [4], 3PCA (N.C. Singha and D.N. Sathyanarayana, unpublished results), benzamide [7].
[c] ph, 1,3-disubstituted phenyl group.

gen bonds and using standard N–H–N distance (3.10 A). The calculated NOE at H6′ for the dimer is 2.8% when the N–H proton is saturated, which is in satisfactory agreement with that observed (2.3%) in the concentrated $CDCl_3$ solution. The structure of the dimer seems to get further support from the appearence of NOE at H2 in the concentrated solution, when H6′ was saturated. In the monomer, H2 is 6.5 A away from H6′ and at such large distances,it is very unlikely to observe NOE. In very dilute solutions, only the monomeric form is predominant.

The ^{1}H NMR spectrum of (**2**) was simulated in good agreement with the experimental spectrum. ^{1}H NMR spectrum in $CDCl_3$ shows that it exists only in one conformation. The large down field shift (1.31 ppm) of H3′ (8.38 ppm) relative to that of H5′ (7.07 ppm) also suggests the coplanarity of the 2-pyridyl ring with the amide group to which it is bonded as in (**1**).

For (**2**) in $CDCl_3$ when the N–H protons are saturated, the NOEs are observed at H2 (7.8%) and at H4 and H6 (2.1%) which are equivalent. A small amount (0.5%) of NOE is also observed at H6′ and H6″, which are equivalent. The NOEs at H2 and H4 indicate that the distance of NH1 proton from H4 is greater than that of NH1 from H2. The molecular conformation of (**2**) inferred from the above discussion is as shown in Fig. 1. It finds support from the fact that H4 and H6 are equivalent and the protons of the ring B1 (H3′ to H6′) are equivalent to the corresponding protons of the ring B2 (H3″ to H6″).

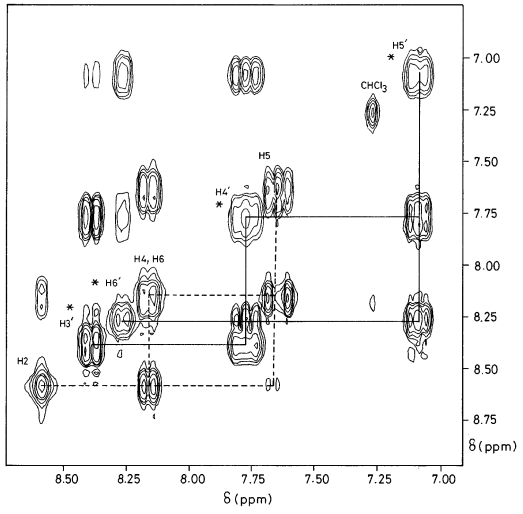


Fig. 2. COSY contour plot of (**2**) in $CDCl_3$.

The ^{13}C chemical shifts of (**1**) and (**2**) (Table 1) for the 2-pyridyl and C=O groups compare well with those of 2NPA, 2NPB [2] and 3PCA (*N*-(3-pyridinyl)carboxamide) (N.C. Singha and D.N. Sathyanarayana, unpublished results) suggesting that the conformation of the 2-pyridyl ring and the amide group is similar in (**1**) and (**2**) consistent with ^1H NMR studies. Comparison of the C3 values in (**1**) and (**2**) with those of 2-aminopyridine (108.5 ppm), 2-(*N*,*N*-diacetylamino)pyridine (123.7 ppm) and 2-(*N*,*N*-dibenzylamino)pyridine (121.8 ppm) [5] indicates that in (**1**) and (**2**) as well as in 2-aminopyridine, 2NPA and 2NPB, the lone pair on the amino nitrogen is conjugated to the pyridine ring while in the diacylated compounds, it is not. This, together with the deshielding of H3 proves that diacylamino group adopts a less sterically hindered conformation with the carbonyl group out of the plane of the pyridine ring, while the other compounds cited adopt a planar conformation.

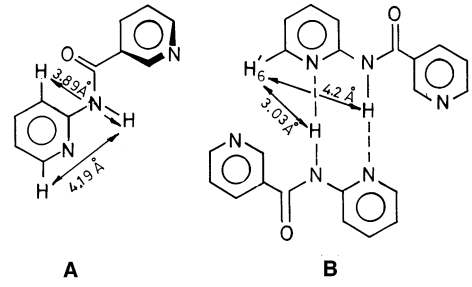


Fig. 3. Dimer structure of (**1**).

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