An NMR study of the tautomerism of 2-acylaminopyridines

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Application of the SIMPLE (secondary isotope multiplet NMR spectroscopy of partially labelled entities) technique to heteroaromatic tautomerism proves that *N*-(pyridin-2-yl)acetamide **1** exists in [^{2}H]chloroform, [$^2H_6$]acetone or [$^2H_6$]benzene solutions as the amide tautomer-rotamer **A-I**. The corresponding amide tautomeric form of *N*-(pyridin-2-yl)benzamide **2** was also found in [^{2}H]chloroform. These results confirm long-established patterns of heteroaromatic tautomerism, and illustrate the utility of SIMPLE in tautomerism studies.

N-(Pyridin-2-yl)acylamides can theoretically exist in three tautomeric structures, each of which can exist in four preferred rotameric forms: (*i*) the acylamino form **A** (rotamers **I–IV**); (*ii*) the hydroxyimino form **B** (rotamers **V–VIII**); and (*iii*) the acylimino form **C** (rotamers **IX–XII**) (Scheme 1). A recent comparison of experimental and simulated UV absorption spectra appeared to indicate that *N*-pyridin-2-ylacetamide **1** exists in non-polar solvents as an equilibrium mixture of tautomeric forms **B-VII** and **B-V**, with **B-VII** predominating.[1,2] These conclusions disagree with those reached by the senior author 35 years ago from basicity studies and UV and IR comparisons with alkylated models,[3] with the generalization made in the definitive monograph on the tautomerism of heterocycles,[4] and *inter alia* with the more recent conclusions of Suciu and Györfi who showed by means of electronic spectra that α-acylamino-*N*-heterocycles in which the acyl group is not powerfully electron-withdrawing, exist in the amido form.[5]

In view of the discordant results obtained in recent work[1,2] we have now reinvestigated the tautomerism of *N*-(pyridin-2-yl)acetamide **1** and *N*-(pyridin-2-yl)benzamide **2** as examples of 2-acylaminopyridines using modern powerful NMR techniques. These results completely vindicate the long-held view that these compounds exist essentially completely in the acylamino form, and demonstrate the power of the SIMPLE NMR technique in unambiguously clarifying tautomeric identities.

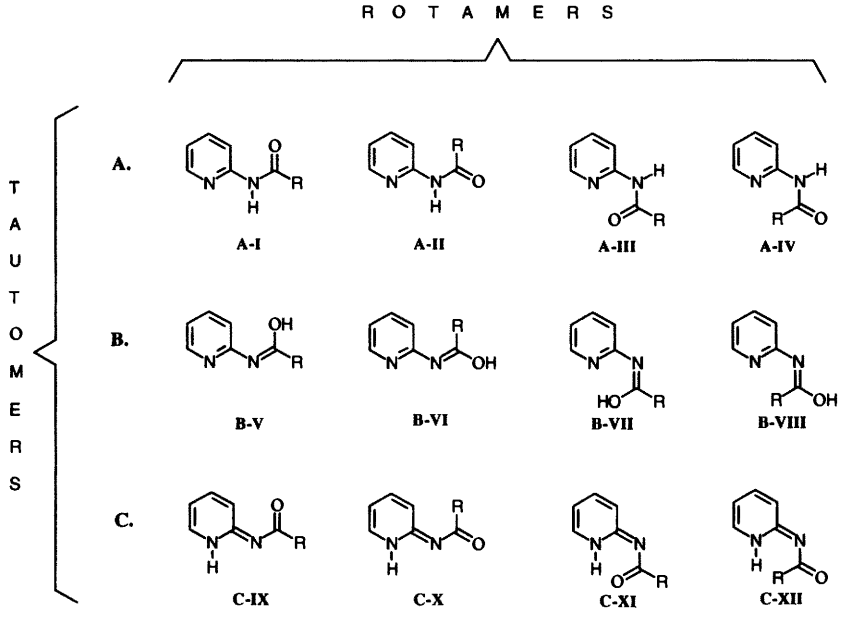
Results and discussion

The ^{1}H and ^{13}C spectra showed that only one tautomeric form is present in detectable concentration in the [^{2}H]chloroform solutions of both **1** and **2**. The ^{1}H spectra of **1** in [$^2H_6$]acetone and [$^2H_6$]benzene were very similar to the ^{1}H spectrum in [^{2}H]chloroform, indicating the presence of a single tautomeric form in all of these solvents.

The ^{1}H and ^{13}C chemical shift assignments for **1** and **2**, as verified by HETCOR experiments,[6] are presented in Table 1.

Definitive evidence was obtained utilizing secondary isotope multiplet NMR spectroscopy of partially labelled entities (SIMPLE). Replacement of the (O/N)H protons by deuterons induces a secondary isotope shift on carbons two or three bonds away, which is observed as a 'splitting' of their signals in the ^{13}C spectrum when this replacement is only partial. The only requirement for the success of this experiment is that the proton–deuterium exchange is slow on the NMR timescale compared with the value of the splitting—DIS (deuterium induced ^{13}C differential isotope shift).

DIS have already been widely used in structural assignments

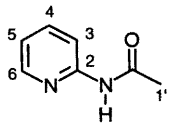


Scheme 1 Possible tautomeric forms of 2-acylaminopyridines

Table 1 NMR data for compounds **1** and **2**

	Compd.	Position 2	3	4	5	6	O/NH	CO	1′	2′	3′	4′
δ_H	**1**	—	8.29	7.72	7.05	8.29	10.39	—	2.21	—	—	—
	2	—	8.40	7.64	6.91	7.95	10.38	—	—	7.92	7.36	7.40
Mult.[a]	**1**	—	d	t	dd	d	br	—	s	—	—	—
	2	—	d	t	dd	d	br	—	—	d	t	t
J/Hz	**1**	—	7.9	7.9	4.4, 7.9	4.4	—	—	—	—	—	—
	2	—	7.9	7.9	4.8, 7.9	4.8	—	—	—	7.8	7.8	7.8
δ_C	**1**	151.8	114.4	138.1	119.1	146.9	—	169.0	24.0	—	—	—
	2	151.6	114.4	138.3	119.4	147.1	—	166.0	134.1	127.3	128.3	128.6
DIS (ppm)	**1**	0.099	0.070	<0.011	<0.011	<0.011	—	0.095	0.044	—	—	
	2	0.087	0.044	<0.006	<0.006	<0.006	—	0.084	0.020	<0.006	<0.006	<0.006

[a] Multiplicity: s = singlet, br = broad, d = doublet, t = triplet.



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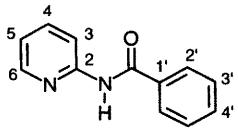

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and in the study of equilibria and hydrogen bonding.[7,8] As compared to protium, deuterium forms bonds which are shorter and of lower energy. A shorter bond implies increased shielding of neighbouring carbon atoms, and this intrinsic effect (IE) has been noticed over two or three bonds. The IE which occurs when protons which are localized (on the NMR timescale) are replaced by deuterons was previously used for ^{13}C chemical shift assignments in carbohydrates[9,10] and peptides[11,12] and was referred to as the SIMPLE technique. Replacement of a proton involved in a fast equilibrium by deuterium produces a shift of the equilibrium in the deuteriated isotopomer towards the form in which the bond formed by the proton (or deuteron) is stronger, or more sterically strained. These equilibrium effects (EE) are observed as shielding or deshielding DIS throughout the molecule. In this paper we follow the convention used by Hansen,[13,14] where a positive DIS denotes shielding, DIS = $\delta_C(H) - \delta_C(D)$.

Partially deuteriated samples of **1** and **2** displayed positive DIS values for the C-2, C-3, CO and C-1′ signals, clearly proving that both compounds exist in [^{2}H]chloroform solutions in the tautomeric form **A**. Comparison of DIS values, measured with an accuracy of 0.011 ppm in the case of **1** and 0.006 ppm in the case of **2**, with those for intrinsic effects in amino acids and peptides[12] indicate an α-effect on C-1 and CO and a β-effect on C-3 and C-1′ (Table 1).

Discrimination between rotamers **I–IV** of tautomer **A** was made on the basis of the δ-value of 3-H. These protons experience strong deshielding (8.29 ppm in **1** and 8.40 ppm in **2**) compared with 6.49 ppm in 2-aminopyridine, 7.29 ppm in *N*,*N*-diacetyl-2-aminopyridine and 7.25 ppm in *N*,*N*-dibenzoyl-2-aminopyridine. Comparison of the δ-values for C-3 in compounds **1** and **2** with those in 2-aminopyridine (108.5 ppm), 2-(*N*,*N*-diacetylamino)pyridine (123.7 ppm) and 2-(*N*,*N*-dibenzoylamino)pyridine (121.8 ppm) indicates that in 2-aminopyridine and compounds **1** and **2** the lone pair on the amino nitrogen is conjugated with the pyridine ring while in the diacylated compounds it is not. This implies that in the diacylated compounds the diacylamino group adopts the less sterically hindered conformation, with the carbonyl groups out of the plane of the pyridine ring. The fact that 3-H is significantly more deshielded in **1** and **2** than in the diacylated derivatives proves that compounds **1** and **2** exist predominantly as tautomer–rotamer **A-I**, in which 3-H experiences an anisotropic deshielding effect from the carbonyl group. Similar effects on 3-H in other acylated 2-aminopyridines have been attributed to the coplanar proximity of the carbonyl group.[15]

Less conclusive attempts to discriminate between tautomers **A**, **B** and **C** in Scheme 1 were also made by searching for polarization transfer (due to long-rang couplings over two or three bonds) from the exchangeable proton bonded to a heteroatom [(O/N)H] to carbons. Tautomer **A** should display polarization transfer to C-2, C-3, CO and C-1′, tautomer **B** to CO and C-1′ and tautomer **3** to C-2, C-3, C-5 and C-6. However, 2D experiments using the long range ^1H–^{13}C correlation pulse sequence developed by Khrishnamurthy[16] failed to detect polarization transfer from (O/N)H to any carbon, in both **1** and **2**. Similar results were obtained by Yanachkov and Wright[17] and were explained by loss of magnetization during the delay required to create antiphase magnetization along the ^1H–^{13}C long-range multiplets. However, they did detect long-range couplings of an NH proton to carbons by employing a one-dimensional selective INEPT experiment.[18] We performed an analogous experiment which showed no polarization transfer from (O/N)H in the case of **1**; in the case of **2**, long-range couplings of (O/N)H with C-3 and CO were detected.

We have preached in the past,[19,20] and we will doubtless preach in the future, that when a chemical or physical technique indicates an unexpected or unusual tautomeric form, all of the evidence should be considered before far-reaching claims are made.

Experimental

Materials

N-(Pyridin-2-yl)acetamide (mp 62 °C, lit.,[21] 60–62 °C) and *N*-(pyridin-2-yl)benzamide (mp 87 °C, lit.,[22] 86 °C) were prepared according to literature procedures. Partially deuteriated samples (69% deuteriation in the case of **1** and 55% deuteriation in the case of **2**) were obtained by heating a *ca.* 1 mol dm^{-3} [^{2}H]chloroform solution (1 cm^3) of the 2-acylaminopyridine (**1** and **2**) with a 1:1 D_2O–H_2O mixture (0.5 cm^3) for 2 min with stirring. The water was decanted off, after which the [^{2}H]-chloroform solution was dried over magnesium sulfate.

NMR

Spectra were recorded on a VARIAN Gemini 300 or a VARIAN VXR 300 instrument, in [^{2}H]chloroform (except where

otherwise specified). Chemical shifts are given in ppm relative to Me_4Si and coupling constants in Hz. ^{13}C spectra in SIMPLE experiments were recorded with a digital resolution of 0.011 ppm for **1** and 0.006 ppm for **2**, in 256 transients, allowing 10 s relaxation time between pulses.

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