

Geminal Coupling Constants ${}^2J(^{15}\text{N}^{13}\text{C})$ in 2-Substituted Pyridines, Measured by Hahn-Echo Extended (HEED) Pulse Sequences

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Pyridines, ${}^{15}\text{N}$ – ${}^{13}\text{C}$ Couplings, Long Range

${}^{15}\text{N}$ – ${}^1\text{H}$ Couplings, ${}^{13}\text{C}$ NMR Spectra,

${}^{15}\text{N}$ Ultra High Resolution NMR

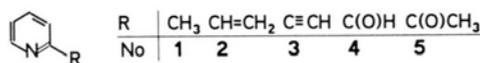
Coupling constants ${}^2J(^{15}\text{N}^{13}\text{C}_R)$ and ${}^nJ(^{15}\text{N}^1\text{H}_R)$ in 2-substituted pyridines [R = Me (**1**), CH=CH₂ (**2**), C≡CH (**3**), C(O)H (**4**), C(O)Me (**5**)] have been measured by using Hahn-echo extended (HEED) pulse sequences for one- (1D) and two-dimensional (2D) ${}^{13}\text{C}/{}^1\text{H}$ NMR (HEED-INEPT, HEED-HETCOR). The magnitude of $|{}^2J(^{15}\text{N}^{13}\text{C}_R)|$ is hardly affected by the hybridization of ${}^{13}\text{C}_R$. ${}^{15}\text{N}$ NMR spectra, measured under conditions of ultra high resolution (UHR) confirm the values ${}^2J(^{15}\text{N}^{13}\text{C}_R)$. 2D ${}^{13}\text{C}/{}^1\text{H}$ HEED-HETCOR experiments show that the sign of ${}^3J(^{15}\text{N}^1\text{H}_R)$ is negative in **1**, whereas the coupling constants ${}^3J(^{15}\text{N}^1\text{H}_R)$ in **4** and ${}^4J(^{15}\text{N}^1\text{H}_R)$ in **3** have a positive sign.

The measurement of coupling constants between rare spin-1/2 nuclei in natural abundance is still a difficult task, in particular for the combination ${}^{15}\text{N}$ – ${}^{13}\text{C}$. Although it is possible to observe ${}^{13}\text{C}$ satellites in ${}^{15}\text{N}$ NMR spectra, this is not straightforward because of the low sensitivity of ${}^{15}\text{N}$ in the NMR experiment. On the other hand, the low intensity (0.18%) of ${}^{15}\text{N}$ satellites in ${}^{13}\text{C}$ NMR spectra complicates their unambiguous assignment next to weak signals arising from ${}^{13}\text{C}$ – ${}^{13}\text{C}$ long range coupling and/or small amounts of impurities.

Recently, Hahn-echo extended (HEED) pulse sequences [1] have been extensively exploited to measure one-bond ${}^{15}\text{N}$ –X coupling constants (e.g., X = ${}^{13}\text{C}$, ${}^{29}\text{Si}$, ${}^{31}\text{P}$, ${}^{119}\text{Sn}$, ${}^{207}\text{Pb}$). These experiments are based on short transverse relaxation times $T_2(\text{X}-{}^{15}\text{N})$ as compared to $T_2(\text{X}-{}^{15}\text{N})$, since scalar relaxation of the second kind is absent in the X/ ${}^{15}\text{N}$ isotopomer. Therefore, provided that there

is no other source of signal broadening, the transverse X-magnetization connected with X– ${}^{15}\text{N}$ coupling is little affected during the time of the Hahn-echo, whereas the X– ${}^{14}\text{N}$ magnetization has decayed to a considerable extent. Depending on the length of the Hahn-echo delay and on the magnitude of scalar X– ${}^{14}\text{N}$ coupling, the parent line can be completely or at least partially suppressed. This allows to take advantage of the full dynamic range of the spectrometer and to distinguish the ${}^{15}\text{N}$ satellites in order to measure coupling constants $J(^{15}\text{N}\text{X})$ as well as isotope induced shifts $\Delta J^{15/14}\text{N}(\text{X})$, all at natural abundance of ${}^{15}\text{N}$ and X (assuming higher NMR sensitivity of X than ${}^{15}\text{N}$). Furthermore, two-dimensional (2D) X/ ${}^1\text{H}$ HEED heteronuclear shift correlations (HEED-HETCOR) allow to measure long range coupling constants ${}^nJ(^{15}\text{N}^1\text{H})$ and to determine relative signs of coupling constants $J(^{15}\text{N}\text{X})$ and $J(^{15}\text{N}^1\text{H})$.

In this work, we have used HEED pulse sequences for the first time to measure two-bond coupling constants ${}^2J(^{15}\text{N}^{13}\text{C}_R)$ in the 2-substituted pyridines C₅H₄N-2-R (**1** to **5**). These were selected to compare the influence of different groups R and the influence of the lone pair of electrons at nitrogen [2, 3] on the magnitude of the geminal coupling constants $|{}^2J(^{15}\text{N}^{13}\text{C}_R)|$.



Relevant NMR data of **1** to **5** are given in Table I. Fig. 1 shows the ${}^{13}\text{C}(\text{CO})$ resonance of **5**, typical of the HEED-INEPT (see Scheme 1) experiments, and in Fig. 2 the HEED-HETCOR experiments is demonstrated for **3**. In the HEED-HETCOR pulse sequence the basic HETCOR

Table I. Chemical shifts $\delta^{15}\text{N}^a$ and coupling constants ${}^2J(^{15}\text{N}^{13}\text{C}_R)^b$, ${}^nJ(^{15}\text{N}^1\text{H}_R)^c$ in the 2-substituted pyridines **1** to **5**.

C ₅ H ₄ N-2-R	$\delta^{15}\text{N}$	${}^2J(^{15}\text{N}^{13}\text{C}_R)$	${}^nJ(^{15}\text{N}^1\text{H}_R)$
No R			
1 CH ₃	–62.5	–9.7	–0.9
2 CH=CH ₂	–70.0	–8.6	n.m. ^d
3 C≡CH	–61.7	–9.8	+0.5
4 C(O)H	–59.0	–14.1	+0.8
5 C(O)CH ₃	–64.7	–10.8	<0.2

^a $\delta^{15}\text{N}$ relative to external neat MeNO₂ ($\Xi(^{15}\text{N}) = 10.136767$ MHz); ^b from HEED-INEPT experiments; accuracy > ± 0.1 Hz; ^c from HEED-HETCOR experiments; accuracy ± 0.1 Hz; ^d n.m. = not measured.

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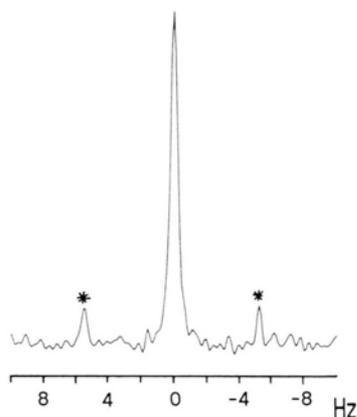


Fig. 1. 125.77 MHz ^{13}C HEED-INEPT NMR spectrum of the carbonyl group in **5** (based on $^2J(^{13}\text{C}^1\text{H}) = 6.3$ Hz) with a Hahn-echo delay $T = 3.0$ s (result of 80 transients, recycle time 5 s, line broadening of 0.1 Hz, spectrometer time 18 min). The ^{15}N satellites according to $^2J(^{15}\text{N}^{13}\text{C}_R) = 10.76$ Hz are marked by asterisks.

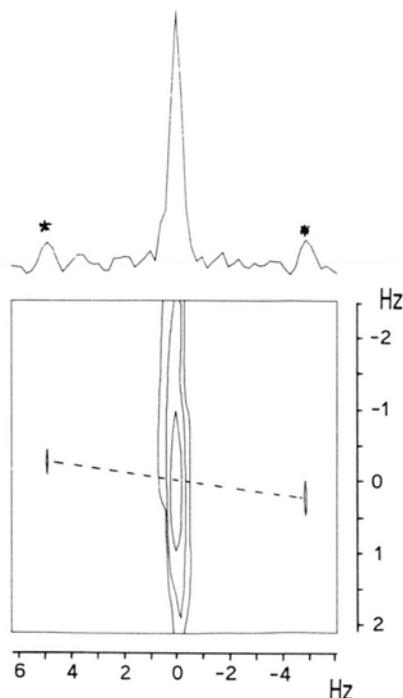


Fig. 2. 125.77 MHz 2D $^{13}\text{C}/^1\text{H}$ HEED-HETCOR experiment, showing the region of the alkynyl carbon atom linked to the pyridine ring in **3** (based on $^2J(^{13}\text{C}\equiv\text{C}^1\text{H}) = 50.0$ Hz), with a Hahn-echo delay of 3.5 s [result of 10 experiments, 400 transients each; with sweep width of 400 Hz in F_2 (^{13}C ; 2 K data points) and 4.5 Hz in F_1 (^1H); recycle time 4 s; zero filling and Gaussian multiplication in both dimensions; spectrometer time 12 h]. The ^{15}N satellites in the F_2 projection are marked by asterisks. The cross peaks, connected by the dashed line, show a negative tilt, indicating opposite signs of $^2J(^{15}\text{N}^{13}\text{C}_R)$ and $^4J(^{15}\text{N}^1\text{H}_R)$.

experiment is used, extended in the same way as for the INEPT pulse sequence shown in Scheme 1. It turned out that sufficient suppression of the parent line (full width at half height 0.7 to 1.0 Hz) can be achieved by using a delay T in the Hahn-echo part in the order of 1.3 to 3.5 s. Much longer delays lead, under the experimental conditions, also to serious loss of transverse magnetization arising from the $^{13}\text{C}/^{15}\text{N}$ isotopomer.

^1H : $-(\pi/2)_x - \Delta/2 - \pi - \Delta/2 - (\pi/2)_y - \tau - (\pi) - \tau -$	Decoupling - - -
^{13}C : - - - $\pi - \Delta/2 - (\pi/2)_x - \tau - (\pi) - \tau -$	T- $(\pi)_x$ -T- Acquisition
Refocused INEPT	Hahn-echo

INEPT: $\Delta/2 = [4J(^{13}\text{C}^1\text{H})]^{-1}$; τ = delay according to number of protons.

Hahn-echo: T = delay for reducing intensity of the parent line.

Scheme 1. INEPT-HEED pulse sequence.

Few examples of two-bond $^{15}\text{N}-^{13}\text{C}$ coupling constants for this type of molecules have been reported. In ^{15}N -labelled 3-methyl-1,2,4-triazine a value of $^2J(^{15}\text{N}^{13}\text{C}_{\text{Me}}) = 9.3$ Hz has been measured [4] and ultra high resolution (UHR) ^{13}C NMR of 2,6-dimethylpyridine gave 9.776 Hz [5]. The $|^2J(^{15}\text{N}^{13}\text{C})|$ values (Table I) for **1**, **2**, **3** and **5** are in a narrow range, the value for **4** is slightly larger. Surprisingly, there is very little variation in the magnitude of $|^2J(^{15}\text{N}^{13}\text{C})|$ with the hybridization of the carbon atom. These data indicate that the presence and the orientation of the lone pair of electrons at the nitrogen atom dominates the two-bond $^{15}\text{N}-^{13}\text{C}$ coupling, the nature of the carbon atom and its substituents being of minor importance. The UHR ^{15}N NMR measurements of **1** to **5** gave the same results for $^2J(^{15}\text{N}^{13}\text{C}_R)$. The ^{13}C satellites corresponding to $^1J(^{15}\text{N}^{13}\text{C})$, $^2J(^{15}\text{N}^{13}\text{C})$ and $^3J(^{15}\text{N}^{13}\text{C})$ in the expected order of magnitude for pyridine carbon atoms [5] were also observed. However, these satellites overlap because of the unsymmetrical substitution of the pyridine ring and their assignment is ambiguous since the isotope induced shifts are not precisely predictable. These measurements are more time-consuming as compared to the HEED-INEPT ^{13}C NMR spectra, and they require rather stringent experimental conditions, in particular if a 500 MHz instrument is used. According to the stereochemical dependence of $^2J(^{15}\text{N}^{13}\text{C})$ [2, 3], a negative sign of $^2J(^{15}\text{N}^{13}\text{C})$ can be safely assumed [reduced coupling constant $^2K(^{15}\text{N}^{13}\text{C}) > 0$; $K(\text{AB}) =$

$4\pi^2 \cdot J(\text{AB}) \cdot (\gamma_A \cdot \gamma_B \cdot h)^{-1}$]. In agreement with the literature [5], the isotope induced shifts $^2\Delta^{15/14}\text{N}(^{13}\text{C})$ are small ($< +1$ ppb for **1**, **2** and **3**, and $+2.0$ for **4** and $+1.5$ ppb for **5**) and positive (*i.e.* the resonance signal of the molecule containing the heavier isotope is shifted to higher frequencies [6]). The $^2\Delta^{13/12}\text{C}(^{15}\text{N})$ values, obtained from the UHR ^{15}N NMR spectra, are also very small ($< +1$ ppb) and positive.

In 2D $^{13}\text{C}/^1\text{H}$ HEED-HETCOR experiments the ^{15}N nucleus serves as a passive spin and therefore small long range coupling constants $^nJ(^{15}\text{N}^1\text{H})$ can be determined from the 2D correlation map. Thus $^4J(^{15}\text{N}^1\text{H}) = 0.5 \pm 0.1$ Hz is clearly resolved in the case of **3** (Fig. 2). Furthermore, the tilt of the cross peaks gives the relative signs [7] of the coupling constants involving the passive spin and the two active spins, $^nJ(^{15}\text{N}^1\text{H})$ and $^2J(^{15}\text{N}^{13}\text{C})$. The positive tilt reveals alike signs in the case of **1**, but in the case of **3** (Fig. 2) and **4** opposite signs follow from the negative tilt.

Experimental

Commercial samples of the pyridine derivatives **1** to **5** were used without further purification. NMR spectra (^{13}C : 125.77 MHz; ^{15}N : 50.5 MHz)

were measured from solutions in C_6D_6 (50% V/V) in 5 mm (o.d.) tubes by using a Bruker AM 500 spectrometer (see also Table I and Fig. 1 and 2). Experimental conditions were close to those described for UHR NMR [5, 8]. Particular care was taken to minimize temperature gradients in the sample owing to dielectric heating by ^1H decoupling. In ^{15}N NMR spectra (low power level in CPD decoupling and long recycle times (up to 20 s), measured by the refocused INEPT pulse sequence [9] based on $^2J(^{15}\text{N}^1\text{H})$), it was then possible to observe line widths in the order of 0.05 Hz (acquisition times > 20 s). Under such conditions, the line widths of the $^{13}\text{C}_R$ resonance signals were never less than 0.7 Hz, mainly as a result of partially relaxed scalar $^{14}\text{N}-^{13}\text{C}$ coupling. The delays for polarization transfer in the 1D and 2D experiments were optimized for the coupling constants $^1J(^{13}\text{C}_R^1\text{H})$ (**1**, **2**, **4**) and $^2J(^{13}\text{C}\equiv\text{C}^1\text{H}) = 50$ Hz (**3**) and $^2J(^{13}\text{C}^1\text{H}) = 6.3$ Hz (**5**). The Hahn-echo delay T was adjusted according to the line width ($\Delta\nu_{1/2}$) of the respective parent signal [$T_2 = (\pi \cdot \Delta\nu_{1/2})^{-1}$], assuming that instrumental contributions to the line widths are small.

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