GRADIENT-ENHANCED INVERSE-DETECTED NMR TECHNIQUES FOR DETERMINATION OF ^{1}H-^{15}N COUPLING CONSTANTS IN 2,2-DIMETHYLPENTA-3,4-DIENAL DERIVATIVES

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Determination of ^{15}N chemical shifts and heteronuclear coupling constants of substituted 2,2-dimethylpenta-3,4-dienal hydrazones is presented. The chemical shifts were determined by gradient-enhanced inverse-detected NMR techniques and ^{1}H-^{15}N coupling constants were extracted from phase-sensitive gradient-enhanced single-quantum multiple bond correlation experiments. Stereospecific behaviour of the coupling constants $^{2}J(^{1}H,^{15}N)$ and $^{1}J(^{1}H,^{13}C)$ has been used to determine the configuration on a C=N double bond. The above-mentioned compounds exist predominantly as *E* isomers in deuteriochloroform.

Key words: 2,2-Dimethylpenta-3,4-dienal; Hydrazones; Inverse-detected NMR spectroscopy; ^{15}N chemical shifts; ^{1}H-^{15}N coupling constants.

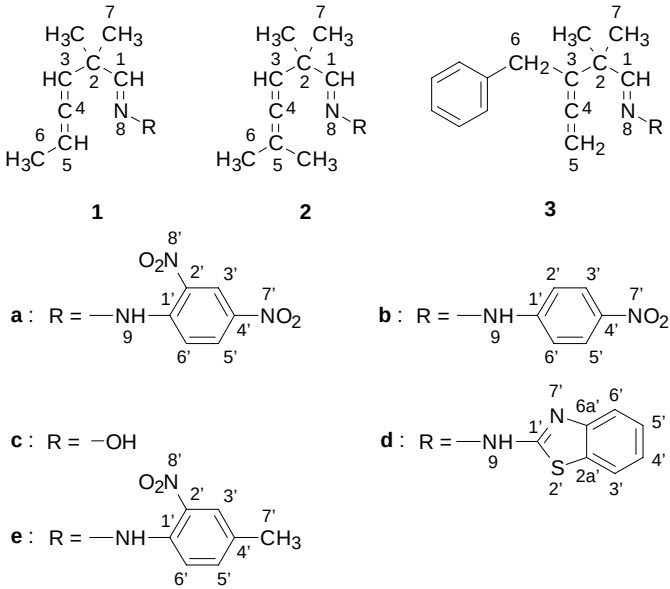
Some derivatives of homoallenyl aldehydes have already been studied and have shown very interesting novel cyclization reactions. Thus, substituted 2,2-dimethylpenta-3,4-dienal azine underwent a thermally initiated isomerization under formation of a novel tetracyclic structure[1]. Hydrazones of 3-substituted 2,2-dimethylpenta-3,4-dienals cyclized *via* the hydrazone nitrogen atom and the central carbon atom of the allenic structure[2]. Cyclization was followed by an oxidation to 5-substituted 5-hydroxy-4,5-dihydropyridazin-3(2*H*)-ones[3]. Preparation and spectral characterization of some substituted hydrazones of title compounds was reported[4,5].

The NMR experiments correlating proton and nitrogen (^{15}N) chemical shifts across several bonds supply valuable information for molecular structure determination of organic compounds. The original experiments based on the direct observation of ^{15}N nuclei have been outdated by *proton*- or *inverse*-detected variants[6]. These *inverse*-detected experiments introduce dramatic increase in sensitivity since highly sensitive ^{1}H nuclei are employed to monitor the spectral parameters of ^{15}N nuclei. Recently, significant improvement of the inverse-detected experiments has been attained by the introduction of pulsed field gradients[6] (PFG). The utilization of PFG proved to be extremely useful in applications optimized to detect the long range scalar interactions. The gradients have been implemented to eliminate the t_1 noise, improve the solvent sup-

pression, remove the spectral artifacts and facilitate observation of very weak interactions across several bonds (*e.g.* ^4J).

The ^{15}N chemical shifts and long-range coupling pathways can be detected by gradient-enhanced HMBC (heteronuclear multiple bond correlation)[7] and HSQC (heteronuclear single-quantum correlation)[8] experiments. The measurements of long-range coupling constants ^nJ is greatly facilitated by a phase-sensitive GSQMBC (gradient-enhanced single-quantum multiple bond correlation) experiment[9].

The results obtained by application of gradient-enhanced experiments for the measurement of ^{15}N chemical shifts, detection of remote connectivities and assessment of ^{1}H-^{15}N long-range coupling constants in 2,2-dimethylpenta-3,4-dienal derivatives **1**–**3** are presented.



EXPERIMENTAL

2,2-Dimethylpenta-3,4-dienal derivatives **1**–**3** were prepared by the reaction of corresponding aldehydes with substituted hydrazines or hydroxylamine[5]. NMR samples were prepared by dissolving compounds in deuteriochloroform. Sample concentrations from miligrams (**2c**) to hundreds of miligrams (**2b**) in 500 μl of $CDCl_3$ were used. The ^{13}C and ^{1}H spectra were referenced to the signal of TMS used as an internal standard. The ^{15}N spectra were referenced to the signal of liquid ammonia used as an external standard at 298 K. NMR spectra were measured on a Bruker Avance DRX spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz and ^{15}N at 50 MHz) at 303 K, δ values are in ppm, *J* coupling constants in Hz. Direct measurements of chemical shifts were carried on 5 mm (^{13}C{^{1}H}) and 10 mm (BB{^{1}H}) probeheads. Heterocorrelation experiments were carried out using a 5 mm triple-resonance probehead (^{1}H{^{13}C/BB}) equipped with a *z*-gradient coil using the following sequences:

^{1}H-^{15}N GHMBC (ref.[10]): relaxation delay 2.3 s, delay for evolution of long-range couplings d6 = 60–120 ms, gradient pulse duration 1 ms, postgradient recovery 100 μs, 2–64 scans were acquired per t_1-increment, block size 4 096 × 512 points, gradient amplitudes G1 : G2 : G3 = 42 : 18 : 30 G/cm (Fig. 1).

^{1}H-^{15}N GSQMBC (ref.[9]): relaxation delay 2.7 s, delay for evolution of long-range couplings d6 = 60–120 ms, gradient ratios G1 : G2 : G3 = 4.8 : 52.8 : ±4.8 G/cm, 2–64 scans acquired per increment, block size 4 096 × 512 (Fig. 1).

Experimental ^{n}J(H,N) and ^{1}J(C,C) Coupling Constants (in Hz)

2,2-Dimethylhexa-3,4-dienal 2,4-dinitrophenylhydrazone (**1a**): ^{3}J(H6′,N9) = 1.6.

2,2,5-Trimethylhexa-3,4-dienal 2,4-dinitrophenylhydrazone (**2a**): ^{3}J(H6′,N9) = 2.1; ^{3}J(H3′,N7′) = 1.4; ^{4}J(H6′,N8′) = 1.7.

2,2,5-Trimethylhexa-3,4-dienal 4-nitrophenylhydrazone (**2b**): ^{1}J(C1,C2) = 50; ^{1}J(C2,C3) = 45; ^{1}J(C3,C4) = 102; ^{1}J(C4,C5) = 103; ^{1}J(C5,C6) = 44; ^{1}J(C2,C7) = 37.

2,2,5-Trimethylhexa-3,4-dienal oxime (**2c**): ^{1}J(C1,C2) = 48; ^{1}J(C2,C3) = 45; ^{1}J(C3,C4) = 102; ^{1}J(C4,C5) = 103; ^{1}J(C5,C6) = 41; ^{1}J(C2,C7) = 36.

2,2,5-Trimethylhexa-3,4-dienal 2-(2-benzothiazolyl)hydrazone (**2d**): ^{3}J(H3′,N7′) = 2.1.

3-Benzyl-2,2-dimethylpenta-3,4-dienal 4-nitrophenylhydrazone (**3b**): ^{3}J(H2′,N9) = 3.1; ^{3}J(H3′,N7′) = 2.4.

3-Benzyl-2,2-dimethylpenta-3,4-dienal 4-methyl-2-nitrophenylhydrazone (**3e**): ^{3}J(H6′,N9) = 1.5; ^{3}J(H6′,N8′) = 1.3.

RESULTS AND DISCUSSION

The signals in the ^{1}H NMR spectra of hydrazones were assigned[5] using gradient-enhanced DQF-COSY (ref.[11]). Complete assignment of ^{13}C resonances was obtained from 2D ^{1}H-^{13}C HSQC and HMBC spectra[5]. ^{1}J(C,C) coupling constants were extracted

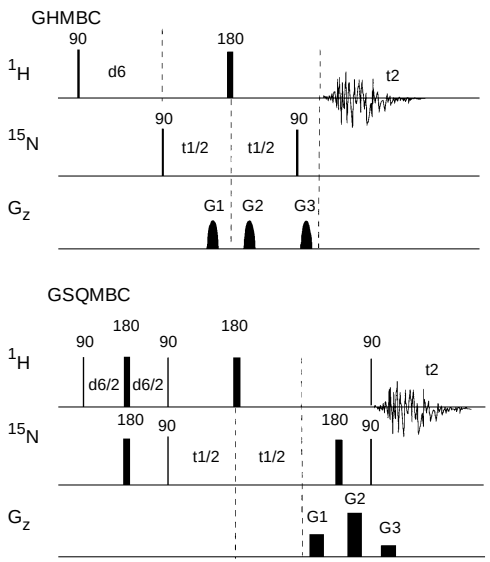


FIG. 1
GHMBC and GSQMBC pulse sequences

either from $^{13}C\{^{1}H\}$ spectra (^{13}C satelites) or from 1D-INADEQUATE. ^{1}H and ^{13}C chemical shifts have been presented recently[5]. ^{15}N chemical shifts and heteronuclear coupling constants are summarized in Tables I and II.

TABLE I
^{1}J(H,C) coupling constants (in Hz) for derivatives **1–3**

Atoms	**1a**	**2a**	**2b**	**2c**	**2d**	**3b**	**3e**
C1–H1	159	160	160	164	160	158	157
C3–H3	167	165	165	166	166	–	–
C5–H5	163	–	–	–	–	167	167
C6–H6	129	128	128	128	128	128	129
C7–H7	129	128	128	128	128	128	128
C2′–H2′	–	–	164	–	–	165	–
C3′–H3′	172	172	167	–	162	166	164
C4′–H4′	–	–	–	–	160	–	–
C5′–H5′	170	170	167	–	158	166	158
C6′–H6′	173	173	164	–	157	165	167
C7′–H7′	–	–	–	–	–	–	127

TABLE II
The values of ^{15}N chemical shifts (δ, ppm) and ^{1}H-^{15}N coupling constants (J (±0.4 Hz) in Hz) for derivatives **1–3**

Compound	δN8	δN9	^{1}J(H9,N9)	δN7′	δN8′	^{2}J(H1,N8)	^{3}J(H1,N9)	^{2}J(H9,N8)
1a	306.3	149.2	97.0	365.4[a]	367.8[a]	3.4	8.5	3.4[c]
2a	305.4	149.5	97.5	365.4[b]	367.7[b]	3.4	8.8	3.1
2b	311.2	143.9	92.0	370.4	–	3.4	8.3	2.5
2c	345.3[c]	–	–	–	–	2.7[c]	–	–
2d	319.4	162.4	[d]	214.6	–	3.7	7.4	[d]
3b	313.2	144.7	91.5	370.8	–	3.5	7.9	3.2
3e	311.8	141.5	96.0	–	371.6	3.7	8.0	2.6

[a,b] The values with the same superscripts may be interchanged. [c] The value may be affected by the poor signal-to-noise ratio. [d] Not observed.

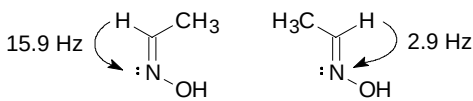
With regard to the unsymmetrical substitution at the C-1 carbon, these compounds can exist as *E* or *Z* isomers. For differentiation between geometrical isomers of hydrazones Bradamante *et al.*[12] suggested utilization of different magnitudes of coupling constants $^1J(^1H,^{13}C)$ of =CHR groups in compounds $C_6H_5NHN{=}CHR$. The values of $^1J(^1H,^{13}C)$ are greater in the *Z* isomer than in the *E* isomer; thus for R = CH_3, $^1J(^1H,^{13}C)$ = 180.6 Hz in *Z* isomer and $^1J(^1H,^{13}C)$ = 160 Hz in *E* isomer were found. These values depend distinctly on the type of substituent R. However, the values of one-bond ^1H-^{13}C coupling constants (~160 Hz) observed for selected compounds **1**–**3** (summarized in Table I) support suggested *E* configuration in solution. For compound **1a** the *E* configuration was also recently found in the crystal[5].

For unequivocal determination of the configuration in solution the stereospecific behaviour of the coupling constants $^2J(^1H,^{15}N)$ was adopted as a generally applicable method. The values of the respective coupling constants are distinctly higher in the "*cis*" orientation of a free electron pair at nitrogen and the corresponding proton[13,14]. The values of coupling constants for planar arrangement of substituents differ very distinctly and are very little affected by the character of substituents[14] (Fig. 2).

All spectra were measured for samples at the natural ^{15}N level (0.36%). In order to enhance the sensitivity of measurements, an *inverse*-detected experiments were used for observation of ^{15}N chemical shifts and $^2J(^1H,^{15}N)$ coupling constants. Pulsed field gradients were applied for selection of coherence transfer pathways to improve the suppression of proton signals from ^1H-^{14}N moieties.

The ^1H-^{15}N GHMBC experiment[10], optimized to detect remote connectivities with scalar coupling constants of approximately 6 Hz, showed a clear interaction of H9 with its directly bonded nitrogen N9 (with the exception of compounds **2c** and **2d**). The same nitrogen is coupled with the hydrogen atom H1 and the H-atoms H2′, H3′, H5′ and H6′, respectively. Responses arising from interactions of the nitrogen N8 with protons H1 and H9 were also observed in the same experiment. Weak interactions of the nitrogen atoms N7′ and N8′ with neighbouring hydrogens were detected ($^nJ(H,N) < 2.5$ Hz).

Absolute mode presentation of HMBC spectra precludes determination of small scalar coupling constants. In order to circumvent limitations of the magnitude mode



4 **5**

FIG. 2
^1H-^{15}N two-bond coupling constants for compounds **4** and **5** (ref.[14])

HMBC, gradient-enhanced single-quantum multiple bond correlation (GSQMBC) experiment[9] have been applied. The phase sensitive ^{1}H-^{15}N GSQMBC experiment enabled to estimate the values of long range coupling constants from the antiphase patterns[15] using analytical approach of Kim and Prestegard[16]. A ^{1}H-^{15}N GSQMBC spectrum of compound **2b** is shown in Fig. 3.

For the two-bond scalar interactions of H1 with N8 the values of ^{2}J(H1,N8) = 2.7–3.7 Hz were obtained. The coupling constant for the three-bond interaction between H1 and nitrogen atom N9 was also measured (^{3}J(H1,N9) = 7.4–8.8 Hz). The two-bond scalar interaction of H9 with N8 has the value of ^{2}J(H9,N8) = 2.5–3.4 Hz. Considering the negative sign of a single-bond proton–nitrogen interaction (^{1}J(H9,N9) = (–)91.5 – (–)97.5 Hz) all the coupling constants discussed above must be positive since antiphase doublets of long-range interactions showed inverted patterns. The values of ^{15}N chemical shifts and ^{1}H-^{15}N coupling constants for compounds **1**–**3** are summarized in the Table II. The range of two-bond coupling constant between atoms H1 and N8 (^{2}J(H1,N8) = 2.7–3.7 Hz) are in the limits typical of *E* configuration on the C=N double bond. It is evident from these values, that the measured compounds exist as *E* isomers in $CDCl_3$ solution.

A generally applicable method for the determination of configuration on the C=N double bond utilizing stereospecific behaviour of the ^{2}J(H,N) coupling constant was used. ^{2}J(H,N) coupling constants were determined by gradient-enhanced inverse-detected NMR experiments. The results presented for 2,2-dimethylpenta-3,4-dienal derivatives clearly demonstrate the power of gradient-enhanced inverse-detected NMR experiments for ^{15}N chemical shift assignment and measurements of long-range coupling constants. The recently developed experiments provide a routine access to parameters (useful for structural studies) previously obtainable only with difficulties.

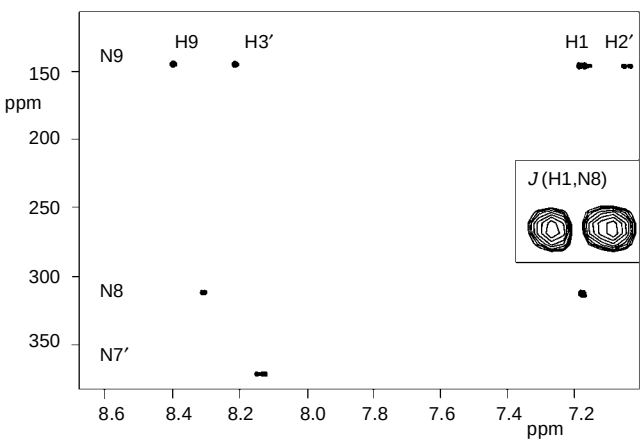


FIG. 3
^{1}H-^{15}N GSQMBC spectrum of compound **2b** (with additional detail of H1-N8 cross-peak)

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