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Synthesis, Tautomerism and Stereochemistry of Spiropyrazolines

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1,3-Dipolar cycloaddition of (*E*)- and (*Z*)-arylidene-1-tetralone derivatives affords *trans*- and *cis*-spiro-1-pyrazolines, respectively, regio- and stereo-selectively in a one-step reaction. These rearrange into spiro-2-pyrazolines on proton catalysis. The relative configurations and conformations of the spiropyrazolines were elucidated by different NMR methods.

KEY WORDS ^{1}H and ^{13}C NMR Spiropyrazolines Conformational equilibria Reaction mechanism

INTRODUCTION

We have previously reported on the stereoselective synthesis and stereochemistry of spiro-1-pyrazolines obtained by 1,3-dipolar addition of diazomethane to different exocyclic α,β-unsaturated ketones, such as 2-arylidene-1-tetralones and 3-arylidene-chromanones, -1-thiochromanones and -flavanones.[1] It was shown that (*E*)-arylidenes afford *trans*-spiro-1-pyrazolines (with respect to the carbonyl and aryl groups) regio- and stereo-selectively, while the same reaction of (*Z*)-3-benzylideneflavanone with diazomethane yielded a *cis*-spiro-1-pyrazoline derivative.[1] This indicated a one-step mechanism of the ring closure. Cycloaddition of diazomethane to chalcones gives 3-benzoyl-4-phenyl-1-pyrazolines, which quickly rearrange to the conjugated 2-pyrazolines.[2] Such a spontaneous tautomerization was not observed with spiro-1-pyrazolines.

This prompted us to carry out further investigations on the one-step mechanism of the ring-closure reaction starting with the corresponding pairs of (*E*)- and (*Z*)-2-(4-chlorobenzylidene)-1-tetralone isomers (**1** and **2**, Scheme 1).

The synthesis, tautomerism and stereochemical analysis of the products obtained (**3**–**6**) are reported in this paper. Although these compounds are racemates, the structural formulae in this paper are restricted to only one enantiomeric series, namely that with the *R* configuration at C-3.

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RESULTS AND DISCUSSION

Syntheses

The addition reaction of (*E*)- (**1**) and (*Z*)-2-(4-chlorobenzylidene)-1-tetralone (**2**) (Scheme 1) afforded stereochemically homogeneous products. A careful chromatographic investigation of the primary products **3** and **4** and the mother liquors revealed no traces of the simultaneous appearance of *trans*- and *cis*-spiropyrazolines, proving the one-step mechanism of the ring closure.

The *cis* compound **4** produced the tautomer **6** after standing for 1 day in $CDCl_3$, whereas **3** remained unchanged after several weeks. Addition of a small amount of trifluoroacetic acid to the $CDCl_3$ solutions of **3** and **4** (same amounts) led to the conversion of **3** to **5** and **4** to **6** within 1 h and 2–3 days, respectively. When these solutions were allowed to stand for 1 week at room temperature, a *cis–trans* isomerization and traces of cyclopropane derivatives formed by nitrogen extrusion[3] were observed.

It should be noted that the numbers in the systematic nomenclature of the 1- and 2-pyrazolines indicate the position of the double bond and differ from the general atom numbering in these molecules (Scheme 1).

Stereochemical analysis

The characteristic ^{1}H chemical shifts and ^{1}H,^{1}H coupling constants, and also the ^{13}C chemical shifts, are

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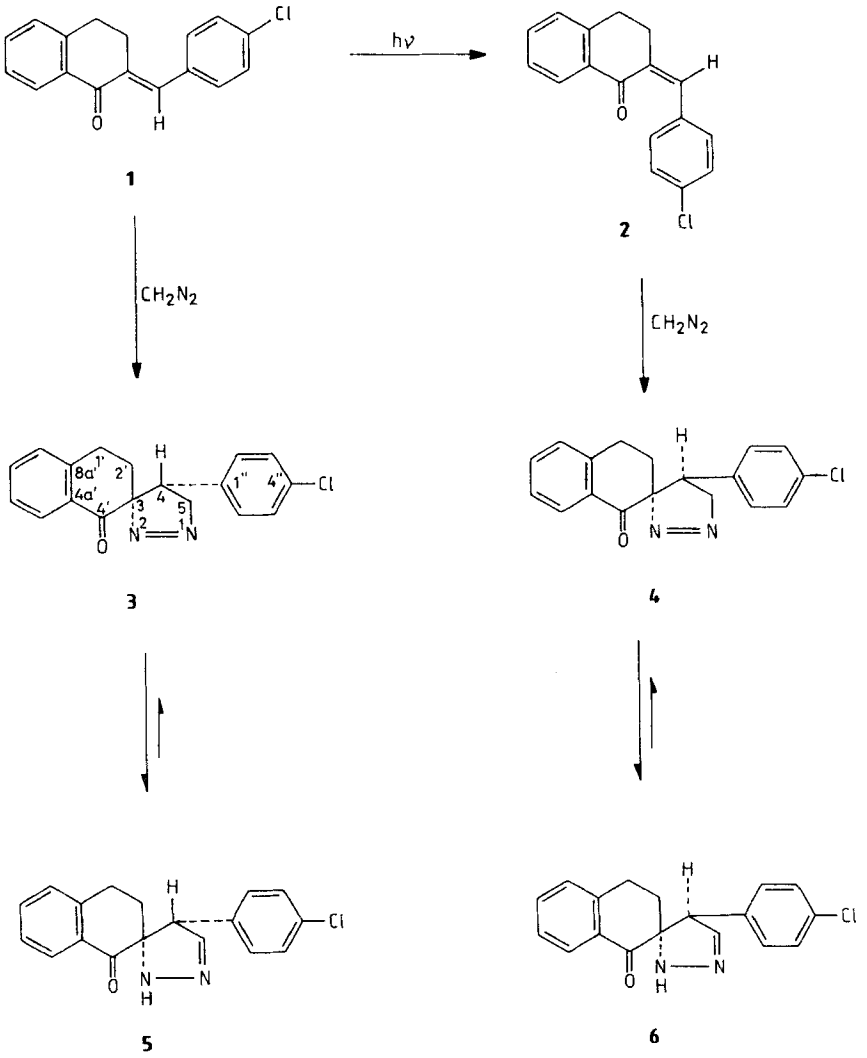


Scheme 1

given in Table 1. Unambiguous ^{13}C signal assignments were achieved by ^{13}C-DEPT, ^{1}H-gated-decoupled and one-dimensional semi-selective INEPT experiments[4] (Table 2).

The configurations in **3** and **5** *vs.* **4** and **6** differ at C-4. The above-mentioned arguments concerning the stereochemistry of the one-step addition mechanism are corroborated by NOE difference experiments (Table 3).[5] Irradiation of the H-4 signals results in NOE intensity enhancements at the H-2′ protons only in the *cis* isomers **4** and **6**. On the other hand, the steric proximity of the H-2″,6″ *ortho* protons of the phenyl ring and the protons on the tetralone moiety in the *trans* isomers **3** and **5** leads to NOEs among them.

The ^{13}C chemical shifts of **3**–**6** gave further evidence for the assignment of *trans* and *cis* isomers. The ^{13}C NMR spectra of *trans* and *cis* isomer pairs exhibit a characteristic difference in the δC-2′ values. The 3.1 and 7.6 ppm upfield shift in **3** and **5**, respectively, is due to the γ-steric interaction between C-2′ and the aryl group attached to C-4. The C-4 signals also show a significant upfield shift in the *trans* isomers.

Scheme 2 illustrates the conformational behaviour of **3** and **4**, which is characterized by ring inversions of the six- (half-chair) and the five-membered rings. The 1-pyrazoline ring exists in envelope conformations X or Y (Scheme 3), where C-4 is out of the plane formed by the other atoms of this ring. Thus, four stereoisomers (A–D) are conceivable in each case; P denotes plus and M minus helicity of the six-membered rings in the enantiomers depicted. Pyrazoline-ring inversion leads to different stereochemical orientations of the H-4 and the two H-5 atoms, as is visible from the Newman projections of the C-5—C-4 bond (Scheme 3), allowing the identification of the predominant conformers by measuring the vicinal $^{1}H,^{1}H$ coupling constants (^{3}J).

It thus emerged that **3** exists predominantly in the A or B conformation, whereas **4** prefers C or D. However, the large couplings $^{3}J(H_{ax}\text{-}1',H_{ax}\text{-}2') = 10.6$ Hz for **3** and 11.1 Hz for **4** clearly indicate that the equilibria of the half-chair conformations are strongly shifted to one side. NOE difference experiments allowed the identification of the conformation in each case; the results are given in Table 3. For example, in **3** there is a close spatial relationships between H_{eq}-2′ and the *ortho* protons of the phenyl substituent (H-2″,6″), proving that **3** adopts conformation B, since in A the *ortho* protons are closer to H_{ax}-1′. On the other hand, **4** prefers confor-

Table 1. ^1H and ^{13}C chemical shifts and characteristic J(H,H) values (Hz) of compounds 3–6

	3	4	5	6
H-4	3.89	3.31	4.57	4.38
H_c-5	4.99	4.76	6.81[a]	6.58[a]
H_t-5	4.97	5.11	—	—
H_{ax}-1′	3.53	3.20	2.76	3.41
H_{eq}-1′	2.84	3.25	2.87	3.07
H_{ax}-2′	1.83	3.07	1.94	2.39
H_{eq}-2′	2.06	2.11	1.84	2.42
H-5′	8.01	7.64	8.04	7.34
H-6′	7.32	7.16	7.32	7.04
H-7′	7.51	7.39	7.48	7.31
H-8′	7.26	7.15	7.17	7.08
H-2″,6″	6.86	6.83	7.10	6.72
H-3″,5″	7.22	7.00	7.30	6.93
NH	—	—	5.66	5.45
^2J(5-CH_2)	18.1	17.8	—	—
^2J(1′-CH_2)	16.5	16.2	18.1	17.8
^2J(2′-CH_2)	13.9	14.3	14.0	14.0
^3J(H-4,H-5$_c$)	8.2	7.7	1.5[a]	1.5[a]
^3J(H-4,H-5$_t$)	9.0	4.5	—	—
^3J(H_{ax}-1′,H_{ax}-2′)	10.6	11.1	5.6	11.7
^3J(H_{ax}-1′,H_{eq}-2′)	4.6	4.1	7.0	4.5
^3J(H_{eq}-1′,H_{ax}-2′)	5.1	7.5	7.0	4.8
^3J(H_{eq}-1′,H_{eq}-2′)	4.9	4.1	5.7	3.0
C-3	100.9	99.2	70.8	74.7
C-4	42.5	46.8	55.7	59.8
C-5	84.7	83.6	146.0	144.5
C-1′	26.5	25.7	25.7	25.6
C-2′	29.6	32.7	28.4	36.0
C-4′	191.6	192.4	195.1	197.2
C-4a′	131.2	131.7	130.1	132.1
C-5′	128.3	127.4	128.6	127.2
C-6′	126.9	126.9	126.8	126.7
C-7′	134.3	133.9	133.8	133.5
C-8′	128.8	128.3	128.7	128.1
C-8a′	142.2	144.2	143.7	141.6
C-1″	137.0	135.0	133.5	133.5
C-2″,6″	129.5	129.6	130.5	130.0
C-3″,5″	128.7	128.3	128.7	128.3
C-4″	133.1	132.9	133.6	133.5

[a] H-5.

mation D, because there is a NOE between H-4 and H_{eq}-2′; in C there would be NOEs between H-4 and H_{eq}-2′ as well as between H-4 and H_{ax}-1.

Further information about the conformational behaviour of the phenyl substituent at C-4 was supplied by selective two-dimensional INEPT experiments[6,7] (Table 4): the J(H-4,C-2″,6″) coupling constants are between 5.4 and 5.7 Hz in all compounds **3–6**, indicating a strong predominance of the coplanar arrangements of the C-4—H-4 bond and the phenyl ring plane.

The characteristic ^1H chemical shift differences of **3** and **4** are in accordance with the stereochemistry shown above. Comparison of the predominant conformer B for the *trans* isomer **3** with D for the *cis* isomer **4** indicates that the deshielding of H-4 in **3** is a consequence of the anisotropic effect of the *peri*-positioned carbonyl group. In **3** the H_{ax}-2′ proton is above the plane of the phenyl group attached to C-4 and exhibits a diamagnetic shift

Table 2. ^1H–^{13}C long-range correlations for compounds 3–6, observed by semi-selective 1D INEPT measurements [J(H,C) = 7 Hz]

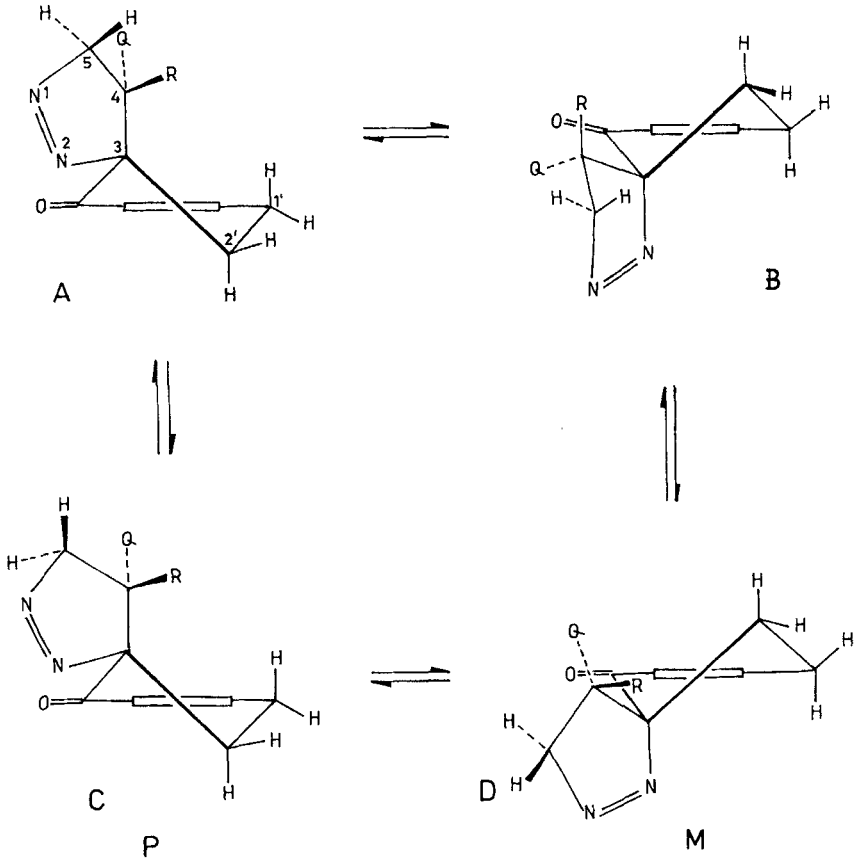
Compound	Proton	Carbon
3	H-4	C-3; C-5; C-4′; C-1″; C-2″,6″
	H_{eq}-1′	C-3; C-2′; C-4a′; C-8′; C-8a′
	H-6′	C-4a; C-5′; C-8′
	H-8′	C-1′; C-4a′; C-6′
	H-2″,6″	C-4; C-4″
4	H-4	C-3; C-5; C-4′; C-1″; C-2″,6″
	H-7′	C-5′; C-8a′
	H-2″,6″	C-4; C-4a
5	H-4	C-3; C-5; C-4′; C-1″; C-2″,6″
	H-7′	C-5′; C-8a′
	H-8′	C-1′; C-4a′; C-6′
	H-2″,6″	C-4; C-4″
6	H-4	C-3; C-5; C-2′; C-4′; C-1′; C-2″,6″
	H_{ax}-1′	C-2′; C-4a′; C-8a′
	H_{eq}-1′	C-3; C-2′; C-4a′; C-8′; C-8a′
	H_2-2′	C-3; C-4′; C-8a′
	H-5′	C-4′; C-4a′; C-7′; C-8a′
	H-7′	C-5′; C-8a′
	H-8′	C-1′; C-4a′; C-6′
	H-2″,6″	C-4; C-4″

Table 3. Results of NOE measurements for compound 3–6

Compound	Proton irradiated	NOE observed (%)
3	H-4	H_2-5 (5.2); H-2″,6″ (7.9)
	H_{eq}-2′	H_{ax}-1′ (5.2); H_{eq}-1′ (2.1); H_{ax}-2′ (22.5); H-2″,6″ (2.5)
	H-2″,6″	H-4 (7.3); H_2-5 (4.3); H_{ax}-2′ (1.3); H_{eq}-2′ (1.1); H-3″,5″ (13.9)
4	H-4	H_t-5 (5.4); H_{eq}-2′ (4.4); H-2″,6″ (7.6)
	H_{ax}-2′	H_2-1′ (>2.6); H_{eq}-2′ (23.1)
	H_{eq}-2′	H-4 (4.1); H_2-1′ (6.2); H_{ax}-2′ (23.8)
	H-2″,6″	H-4 (6.2); H_c-5 (4.8); H-3″,5″ (8.3)
5	H-4	H-5 (3.0); H-2″,6″ (7.7)
	H_{ax}-1′	H_{eq}-1′ (>8.0); H_{eq}-2′ (2.6); H-8′ (3.5)
	H-2″,6″	H-4 (6.5); H_{ax}-1′ (1.3); H_{eq} – 2′ (1.5); H-3″,5″ (>10.5)
6	H-4	H-5 (2.4); H_{ax}-1′ (4.8); H_2-2′ (4.0); H-2″,6″ (6.8)
	H-5	H-4 (1.5)
	H_{ax}-1′	H-4 (5.4); H_{eq}-1′ (19.1); H_2-2′ (3.2); H-8′ (1.7); H-2″,6″ (3.3)
	H-2″,6″	H-4 (7.3); H_{ax}-1′ (4.0); H-3″,5″ (7.2)

Table 4. Results of the 2D semi-selective INEPT measurements of compounds 3–6 [J(H-4,C) (Hz)]

Compound	3	4	5	6
^2J(H-4,C-3)	2.9	3.7	3.2	
^2J(H-4,C-5)	2.0		5.9	6.3
^2J(H-4,C-1″)	4.9	5.1	6.5	6.4
^2J(H-4,C-2′)				7.1
^3J(H-4,C-4′)	4.4	3.9	5.8	4.1
^3J(H-4,C-2″,6″)	5.6	5.4	5.6	5.7



3 R = 4-chlorophenyl, Q = H

4 R = H, Q = 4-chlorophenyl

Scheme 2

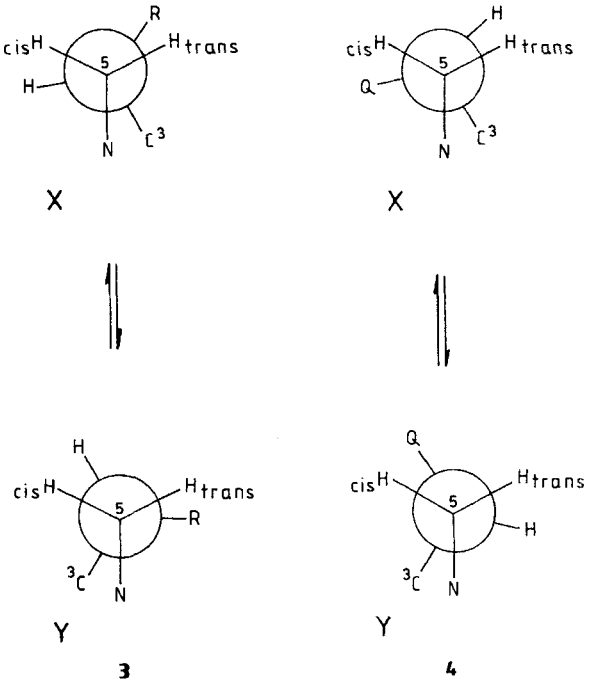
of 1.24 ppm if compared with the corresponding proton in **4**.

The formation of 2-pyrazolines from 1-pyrazolines can be demonstrated by observing the NH protons (**5**, $\delta = 5.66$; **6**, $\delta = 5.45$) and the paramagnetic shift of the H-5 signal. Moreover, C-5 is sp^2-hybridized, now exhibiting chemical shifts around 145 ppm and a characteristic ^1J(C,H) value of 192 Hz.

The $^3J(H_{ax}\text{-}1',H_{ax}\text{-}2') = 11.7$ Hz coupling constant measured for **6** proves that the equilibrium of half-chair conformers is entirely shifted to one side, whereas the value of 5.6 Hz measured for the same coupling in **5** leads to the conclusion that here this ratio is near to 1.

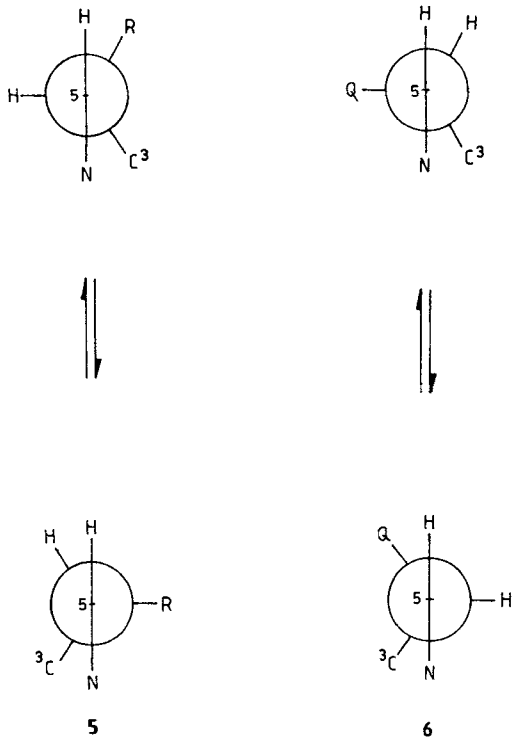
The 2-pyrazoline rings can adopt two envelope conformations where C-3 is out of the plane formed by the other atoms of this ring. The value of ^3J(H-4,H-5) = 1.5 Hz obtained for **5** and **6** indicate the preference of conformers where the dihedral angle between H-4 and H-5 is nearly 90°, which is obvious from Newman projection of the C-5—C-4 bond (Scheme 4).

Determination of the preferred conformation of **6** was achieved by the NOE difference measurements. Irradiation of the H-2″,6″ *ortho* protons results in NOE for H_{ax}-1′ proving the predominance of a half-chair conformer where the C-4 atom occupies the axial position. All this proves that the proton-catalysed isomerization of spiro-1-pyrazoline **4** to spiro-2-pyrazoline **6** is con-



R = Q = 4-chlorophenyl

Scheme 3



Scheme 4

nected with a significant change in the conformational equilibrium.

EXPERIMENTAL

(*E*)-2-(4-Chlorobenzylidene)-1-tetralone (**1**) and (*Z*)-2-(4-chlorobenzylidene)-1-tetralone (**2**) used as starting materials were prepared by known procedures.[8]

Synthesis of Spiropyrazolines 3 and 4

A mixture of compound **1** or **2** (1.0 g), diazomethane (*ca.* 5 mol equivalents), anhydrous diethyl ether (20.0 ml) and anhydrous acetone (30.0 ml) was left to stand in a refrigerator for 48 h, the solvent was evaporated under reduced pressure and the residue was crystallized from methanol to afford 0.94 g (81.7%) of *trans*-(1)-3,4,4',5'-tetrahydro-4'-(4-chlorophenyl) - spiro[naphthalene - 2(1H),3'-[3H]pyrazol-1-one (**3**) from **1**, m.p. 121 °C, and 0.9 g (77.8%) of *cis*-(±)-3,4,4',5'-tetrahydro-4'-(4 - chlorophenyl) - spiro[naphthalene - 2(1H),3' - [3H] - pyrazol]-1-one (**4**) from **2**, m.p. 153 °C. Analysis: $C_{18}H_{15}ClN_2O$ (M.W. 310.75) requires C 69.5, H 4.8; found for **3**, C 69.6, H 4.8 and for **4**, C 69.5, H 4.9%.

Spectra

All NMR spectra were obtained on a Bruker AM-400 spectrometer at room temperature in $CDCl_3$. Chemical shifts are given on the δ scale; the ^1H NMR spectra are referenced to internal TMS and the ^{13}C NMR spectra to the solvent ($\delta_{CDCl_3} = 77.0$ ppm). In the 1D measurements 64K data points were used for the FID. A delay time of 7 s was applied for homonuclear NOE experiments. The 1D semi-selective INEPT measurements[4] were optimized for $J(C,H) = 7$ Hz coupling and 25 Hz selectivity. In the 2D semi-selective INEPT measurements the data matrices were 8K × 64K data points, and the spectral width in the F_1 (proton) dimension was 16 Hz. Selected traces were zero-filled to give a final digital resolution of 0.06 Hz.

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