MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 209–212 (1997)

Reference Data

Discrimination of Structural Isomers of *N*-Methylated and *N*-*tert*-Butylated Tetrazoles by ^{13}C and ^{15}N NMR. Long-Range ^{15}N,^{1}H Coupling Constants

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Natural abundance ^{13}C and ^{15}N NMR studies were carried out on a series of *N*-methylated and *N*-*tert*-butylated tetrazoles. Long-range ^{13}C,^{1}H and ^{15}N,^{1}H NMR coupling constants together with $^{1}J(^{15}\text{N},^{13}\text{C})$ allowed unequivocal assignments of ^{13}C and ^{15}N chemical shifts for isomeric 1,5- and 2,5-disubstituted tetrazoles. © 1997 by John Wiley & Sons, Ltd.

Magn. Reson. Chem. **35**, 209–212 (1997) No. of Figures: 1 No. of Tables: 5 No. of References: 9

KEY WORDS ^{13}C NMR; ^{15}N NMR; long-range ^{13}C,^{1}H and ^{15}N,^{1}H coupling constants; *N*-methylated and *N*-*tert*-butylated tetrazoles

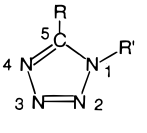
Received 5 June 1996; revised 2 September 1996; accepted 11 September 1996

INTRODUCTION

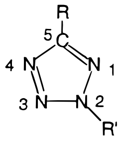
The identification of structural isomers of alkylated tetrazole and its 5-substituted derivatives has been the focus of many investigations, including ^{1}H, ^{13}C and ^{15}N NMR methods.[1] In previous ^{15}N NMR studies the chemical shift assignments were not straightforward and attempts based upon MO electron density calculations led to contradictory results.[1,2] Long-range ^{13}C,^{1}H and ^{15}N,^{1}H[3] coupling constants could provide more information in terms of unambiguous identification and structure elucidation of isomeric tetrazoles. Accordingly, we performed a detailed ^{13}C and ^{15}N NMR study of a series of methylated (**1**–**7**) and *tert*-butylated (**8**–**14**) tetrazoles. In the case of **1**–**7** we prepared ^{13}C labelled *N*-methylated compounds, which allowed us also to observe ^{13}C,^{13}C and ^{15}N,^{13}C coupling constants.

RESULTS AND DISCUSSION

The ^{1}H and ^{13}C NMR chemical shifts for **1**–**14** are given in Table 1. In the case of 5-H-tetrazole and 5-*tert*-butyltetrazole we obtained only the 1-methyl isomers **1a** and **3a**. For **2** and **4**–**7** the methyl protons of the 1-isomers are slightly more shielded by 0.15–0.53 ppm compared with their 2-substituted analogues, but for the *tert*-butyl protons of the isomers of **8**–**14** no such consistency was observed.



1a-14a



2b, 4b-14b

Compound	R′	R
1	Me	H
2	Me	Me
3	Me	t-Bu
4	Me	cyclopropyl
5	Me	Ph
6	Me	CH_2Ph
7	Me	$(CH_2)_2Ph$
8	t-Bu	H
9	t-Bu	Me
10	t-Bu	t-Bu
11	t-Bu	cyclopropyl
12	t-Bu	Ph
13	t-Bu	CH_2Ph
14	t-Bu	$(CH_2)_2Ph$

Carbon chemical shift assignments were made on the basis of signal intensities, analysis of ^{13}C,^{1}H NMR coupling patterns, including selective proton decoupled experiments, and literature data.[4,5] For all pairs of isomers, the largest difference in carbon chemical shifts was observed for C-5 (Table 1), which for the 2,5-isomer resonates 9.20–12.20 ppm to higher frequency relative to the 1,5-isomer. The isomeric methylated tetrazoles **2** and **4**–**7** could be distinguished on the basis of long-range ^{13}C,^{1}H NMR coupling constants involving C-5 and the protons of the methyl substituent at N-1 or N-2 (Table 2), as in the case of N-1 substitution we observed $^{3}J_{\text{C-5, HMe}}$ (2.1–2.8 Hz). For the 2-isomers $^{4}J_{\text{C-5, HMe}}$ was detected only in **5b** and was much smaller than $^{3}J_{\text{C-5, HMe}}$ in **5a**. The values of the chemical shifts, $^{1}J_{\text{CH}}$ coupling constants and substitution chemical shifts of the aromatic carbons for **5a**,**b** and **12a**,**b** are given in Table 3. The largest differences for pairs of isomers are observed for the chemical shifts of C-1′ and C-2′. The $^{1}J_{\text{CH}}$ coupling constants in **5a**,**b** and **12a**,**b** (160.9–163.2 Hz) are slightly greater than those for **6a**,**b**, **7a**,**b**, **13a**,**b** and **14a**,**b** (147–160 Hz), in which the tetrazole and phenyl rings are separated by one or two methylene groups. Substituent carbons attached to N-1 are more shielded than those attached to N-2 atoms in the **2**, **4**–**7** and **8**–**14** series.

Absolute values of $^{1}J_{\text{CN}}$ coupling constants for **1**–**7** are given in Table 4. The signs of the constants are presumably negative[6] and the absolute values of $^{1}J_{\text{C, N-1}}$ are smaller than the corresponding $^{1}J_{\text{C, N-2}}$ by 1.9–2.1 Hz. Table 4 also contains the magnitudes of the ^{13}C,^{13}C coupling constants in **1**–**7**. Vicinal transoid couplings in **2b** and **4b**–**7b** are slightly larger than or equal to the geminal couplings in **1a**–**7a**, and the magnitudes resemble the couplings found in aromatic compounds with aliphatic substituents.[7]

The ^{15}N NMR chemical shifts and the absolute values of ^{15}N,^{1}H NMR coupling constants are presented in Table 5. Our assignments were based mostly on the analysis of ^{15}N,^{1}H NMR coupling patterns with the use of selective proton decoupling where necessary. In previous reports the assignments were connected with the assumption that N-1 and N-4 in general resonate at lower frequency and N-2 and N-3 resonate at higher frequency in tetrazoles and that alkyl substitution results in significant shifting of the pyrrole-type nitrogen resonance to lower frequency. However, relative positions of the signals were not established unambiguously. For an extensive series of tetrazoles it was shown that ^{15}N NMR chemical shifts correlate well with the electron densities at the nitrogen atoms,[1] but in the case of 2,5-dimethyltetrazole (**2b**) different MO methods resulted in contradictory assignments concerning the relative positions of the N-3 and N-4 signals.[1,2] In the proton-coupled spectrum of **2b** both the N-3 and N-4 signals appear as quartets with ^{15}N,^{1}H coupling constants that are close in magnitude (Table 5), supposedly coupled to the protons of *N*-Me and *C*-Me groups, respectively. Irradiation of the *C*-Me protons at 2.11 ppm affected the lower frequency N signal (−48.00 ppm), turning it into a singlet, whereas for the lower frequency N signal the splitting was preserved. This agrees with the results reported in Ref. 2. Unambiguous ^{15}N NMR chemical shift assignments in tetrazoles require coupling pattern analysis and cannot be based upon the MO calculations of electron densities alone. It should be noted that for **9b**, **10b**, **12b** and **14b** we detected four-bond ^{15}N,^{1}H couplings between *tert*-butyl protons and N-3, which were also confirmed by selective proton decoupling. The ^{15}N NMR chemical shifts become increasingly more negative in the order N-3 < N-2 < N-4 < N-1 for 1,5- and N-3 < N-4 < N-1 < N-2 for 2,5-disubstituted tetrazoles.

^{1}H and ^{13}C chemical shifts can be used to differentiate between isomeric 1,5- and 2,5-disubstituted tetrazoles only in special circumstances. In contrast, the application of ^{15}N chemical shifts for this purpose is general. This work demonstrates that the ^{13}C and ^{15}N

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CCC 0749–1581/97/030209–04 $17.50

Table 1. ^1H and ^{13}C NMR chemical shifts (δ, ppm) for compounds 1–14, with proton chemical shifts (Hz) in parentheses[a]

Compound	$Me_{R'}$	$C_{t\text{-}Bu}$	C-5	R
1a[b]	33.80 (3.9)	—	143.20 (8.7)	—
2a	32.72 (3.7)	—	151.42	Me: 7.83 (2.2)
2b	38.46 (3.9)	—	162.00	Me: 9.86 (2.1)
3a	35.69 (4.1)	—	160.76	$Me_{t\text{-}Bu}$: 28.22 (1.4); $C_{t\text{-}Bu}$: 30.85
4a	32.48 (3.8)	—	156.55	Cyclopropyl: 2.84(CH); 7.71(CH_2) (1.6, 0.7–0.9)
4b	38.43 (3.9)	—	167.80	Cyclopropyl: 5.52(CH); 7.49(CH_2) (1.6, 0.7–0.9)
5a	34.03 (4.0)	—	153.18	Ph: 122.75; 127.52; 128.07; 130.05 (7.3–7.6)
5b	38.35 (4.2)	—	163.76	Ph: 125.57; 126.43; 127.86; 129.18 (7.3–7.6, 8.1)
6a	32.50 (3.7)	—	153.08	CH: 28.36 (4.1) Ph: 126.35; 127.57; 127.89; 133.14 (7.0–7.2)
6b	38.12 (4.1)	—	164.37	CH_2: 30.53 (4.0) Ph: 125.72; 127.53; 127.74; 135.95 (7.0–7.2)
7a	32.20 (3.3)	—	153.88	CH_2CH_2: 24.28; 32.53 (2.2, 2.7) Ph: 125.94; 127.62; 127.92; 138.75 (6.7–6.9)
7b	38.37 (3.8)	—	165.14	CH_2CH_2: 26.36; 33.17 (2.2, 2.7) Ph: 125.45; 127.54; 127.67; 139.75 (6.7–6.9)
8a[c]	29.35 (1.6)	59.40	139.81 (8.6)	—
8b[b]	28.98 (1.7)	63.66	152.02 (8.4)	—
9a	28.89 (1.7)	60.03	150.20	Me: 11.43 (2.7)
9b	28.62 (1.7)	62.69	161.40	Me: 10.24 (2.5)
10a	30.32 (1.7)	62.25	160.93	$Me_{t\text{-}Bu}$: 30.62 (1.5); $C_{t\text{-}Bu}$: 32.34
10b	28.60 (1.6)	62.61	173.11	$Me_{t\text{-}Bu}$: 28.92 (1.3); $C_{t\text{-}Bu}$: 30.81
11a	28.69 (1.4)	59.70	155.41	Cyclopropyl: 4.27(CH); 8.51(CH_2) (0.6–0.8, 1.8)
11b	28.37 (1.3)	62.41	166.96	Cyclopropyl: 5.79(CH); 7.44(CH_2) (0.6–0.8, 1.8)
12a	29.93 (1.6)	61.45	153.38	Ph: 126.84; 129.30; 128.03; 130.07 (7.2–7.3)
12b	28.85 (1.8)	63.30	163.93	Ph: 126.27; 127.44; 128.31; 129.55 (7.2–7.3, 8.1)
13a	28.82 (1.4)	60.26	151.87	CH_2: 30.42 (4.22) Ph: 126.41; 127.56; 128.01; 134.50 (6.9–7.1)
13b	28.38 (1.4)	62.51	163.82	CH_2: 30.99 (4.00) Ph: 125.84; 127.70; 127.91; 136.29 (6.9–7.1)
14a	29.17 (1.6)	60.06	153.24	CH_2CH_2: 27.74, 33.26 (3.0–3.2) Ph: 126.28; 127.95; 128.34; 139.72 (7.0–7.2)
14b	28.82 (1.6)	62.83	164.82	CH_2CH_2: 27.02, 33.78 (3.0–3.2) Ph: 125.83; 128.04; 128.04; 140.38 (7.0–7.2)

[a] Chemical shifts and coupling constants are accurate to ±0.01 ppm and ±0.1 Hz, respectively.
[b] $^1J_{C\text{-}5,\,H\text{-}5} = 217.3$ Hz.
[c] $^1J_{C\text{-}5,\,H\text{-}5} = 214.1$ Hz for **8a** and 211.9 Hz for **8b**.

NMR chemical shifts for each isomer can be unequivocally assigned by consideration of the magnitudes of $^{15}N,^1H$, $^{13}C,^1H$ and $^{15}N,^{13}C$ NMR coupling constants.

EXPERIMENTAL

Methylated tetrazoles **1**–**7** were synthesized by alkylation of 5-substituted tetrazoles with ^{13}C-labeled iodomethane.[8] *tert*-Butylation of 5-substituted tetrazoles was performed as described in the literature.[9] ^1H and $^{13}C\{^1H\}$ NMR spectra of 50–100 mg ml^{-1} solutions of **1**–**14** in $CDCl_3$ were recorded on a General Electric QE-300 NMR spectrometer, operating at 300.16 and 75.48 MHz, respectively, at ambient temperature, in 5 mm tubes, with TMS as internal standard. $^{13}C,^1H$ NMR coupling constants were directly measured from ^{13}C NMR proton coupled spectra, recorded on a Varian Unity-plus 500 NMR spectrometer (125.70 MHz) in 5 mm tubes, with a 128 kHz spectral width, 3 s interpulse delay, 45° flip angle and zero-filling to 524 288 data points with final resolution of 0.06 Hz per point. Signs of the constants were not measured.

^{15}N NMR spectra of 500–1000 mg ml^{-1} of **1**–**14** in $CDCl_3$ were obtained on a Varian Unity-plus 500 NMR spectrometer, operating at 50.66 MHz, in 10 mm tubes, at ambient temperature. The ^{15}N NMR chemical shifts were measured relative to external nitromethane. Spectral parameters were spectral width 36 kHz, 20 s interpulse delay, 45° flip angle, 128K data points and zero-filling with final resolution of 0.07 Hz per point.

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Table 2. ^{13}C,^{1}H coupling constants (Hz) of C-5 for compounds 1–7

Compound	^{2}J(C-5, H_R)	^{3}J(C-5, H_R)	^{3}J(C-5, H_{Me})
1a	—	—	2.2
2a	7.2	—	2.1
2b	7.2	—	—
3a	—	m[b]	m
4a	m	m	m
4b	m	m	m
5a	—	1.5	2.8
5b[a]	—	4.1	—
6a	7.9	—	2.1
6b	8.0	—	—
7a	m	m	m
7b	m	m	m

[a] $^{4}J_{\text{C-5, HMe}} = 0.75$ Hz.
[b] m = Multiplet.

Table 4. Absolute values of the ^{13}C,^{1}H, ^{13}C,^{13}C and ^{13}C,^{15}N NMR coupling constants (Hz) of methyl carbons for compounds 1–7

Compound	$^{1}J_{CH}$	$^{1}J_{CN}$	$^{2}J_{CC}$	$^{3}J_{CC}$
1a	143.6	10.2	3.3	—
2a	142.8	11.4	3.1	—
2b	143.2	13.5	—	3.1
3a	142.8	10.4	2.3	—
4a	142.8	11.4	2.9	—
4b	143.3	13.5	—	3.1
5a	143.3	11.0	2.6	—
5b	143.7	13.0	—	3.0
6a	142.8	11.0	2.8	—
6b	143.4	13.1	—	3.1
7a	142.8	11.3	3.1	—
7b	143.4	13.2	—	3.1

Table 3. ^{13}C NMR chemical shifts (δ, ppm), $^{1}J_{CH}$ coupling constants (Hz) and substitution chemical shifts (relative to benzene, 128.50 ppm) of the phenyl carbons of compounds 5a,b and 12a,b

	5a	5b	12a	12b
C-1′	122.75	126.43	126.84	127.44
C-2′	127.52	125.57	129.30	126.27
^{1}J(C-2′, H-2′)	161.7	163.2	162.0	161.5
C-3′	128.07	127.86	128.03	128.31
^{1}J(C-3′, H-3′)	162.2	161.4	162.2	160.9
C-4′	130.05	129.18	130.07	128.31
^{1}J(C-4′, H-4′)	161.9	163.0	161.9	160.9
ipso-	−5.75	−2.07	−1.66	−0.81
ortho-	−0.98	−2.93	+0.8	−2.23
meta-	−0.43	−0.64	−0.47	−0.19
para-	+1.55	+0.68	+1.57	+1.05

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Table 5. ^{15}N NMR chemical shifts (δ, ppm) and $^{15}N,^{1}H$ NMR coupling constants (Hz) for compounds 1–14

Compound	N-1	N-2	N-3	N-4
1a	−151.35 d, $^{2}J = 9.3$ q, $^{2}J = 2.0$	−8.29 m	14.29 d, $^{3}J = 3.0$	−48.64 d, $^{2}J = 12.1$
2a	−153.67 m	−7.49 q, $^{3}J = 1.9$	10.19 s	−52.06 q, $^{3}J = 1.9$
2b	−75.81 m	−103.62 q, $^{2}J = 2.3$	2.03 q, $^{3}J = 1.5$	−48.00 q, $^{3}J = 1.1$
3a	−156.81 m	−3.02 q, $^{3}J = 1.7$	8.03 s	−50.90 s
4a	−154.22 q, $^{2}J = 1.8$	−7.68 q, $^{3}J = 1.4$	9.18 s	−58.88 d, $^{3}J = 2.1$
4b	−81.00 m	−105.01 q, $^{2}J = 2.2$	1.23 q, $^{3}J = 1.8$	−53.53 d, $^{3}J = 1.3$
5a	−156.19 q, $^{2}J = 1.9$	−5.26 q, $^{3}J = 1.8$	11.39 s	−50.36 s
5b	−79.49 q, $^{3}J = 1.7$	−102.08 q, $^{2}J = 2.3$	3.15 q, $^{3}J = 1.6$	−51.83 s
6a	−151.15 q, $^{2}J = 2.2$	−2.41 q, $^{3}J = 2.2$	14.63 s	−44.11 m
6b	−71.79 q, $^{3}J = 1.7$	−99.93 q, $^{2}J = 2.2$	5.97 q, $^{3}J = 1.1$	−46.22 m
7a	−153.67 m	−7.45 q, $^{3}J = 1.7$	10.94 s	−51.39 t, $^{3}J = 1.9$
7b	−75.59 m	−103.71 m	2.31 q, $^{3}J = 1.2$	−48.01 t, $^{3}J = 1.4$
8a	−117.43 m	−11.36 d, $^{3}J = 1.1$	13.77 d, $^{3}J = 3.4$	−50.39 m
8b	−76.57 d, $^{2}J = 15.3$	−71.52 m	−2.18 s	−48.91 d, $^{2}J = 12.6$
9a	−125.00 m	−7.55 s	5.54 s	−48.62 q, $^{3}J = 2.2$
9b	−80.74 q, $^{3}J = 2.3$	−73.20 dec, $^{3}J = 2.3$	−1.52 dec, $^{4}J = 0.8$	−51.14 q, $^{3}J = 1.9$
10a	−124.18 m	−2.17 s	0.32 s	−46.06 s
10b	−82.82 s	−74.80 dec, $^{3}J = 2.5$	−2.64 dec, $^{4}J = 0.6$	−54.01 s
11a	−124.42 m	−8.03 s	3.34 s	−55.21 d, $^{3}J = 2.2$
11b	−85.65 d, $^{3}J = 1.2$	−74.67 dec, $^{3}J = 2.6$	−2.46 s	−57.28 d, $^{3}J = 1.7$
12a	−122.51 m	−2.87 s	6.73 s	−44.89 s
12b	−84.06 s	−71.92 dec, $^{3}J = 1.7$	−0.60 dec, $^{4}J = 0.7$	−54.51 s
13a	−124.70 m	−6.49 s	7.14 s	−44.75 t, $^{3}J = 1.8$
13b	−79.71 t, $^{3}J = 2.2$	−72.54 m, $^{3}J = 2.3$	−0.60 s	−49.71 t, $^{3}J = 3.0$
14a	−125.17 m	−8.38 s	5.83 s	−47.87 t, $^{3}J = 0.6$
14b	−80.58 t, $^{3}J = 1.2$	−73.28 dec, $^{3}J = 2.6$	−1.38 dec, $^{4}J = 0.1$	−51.09 t, $^{3}J = 0.8$