# A Carbon-13 and Proton Nuclear Magnetic Resonance Study of Annular Tautomerism and Interannular Conjugation in Some Substituted-5-aryltetrazoles

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A comparison of $^{13}C$ spectra for a series of substituted 5-phenyltetrazoles. ($RC_6H_4$: R = H, *p*-Me, *p*-$NO_2$, *o*-$NO_2$), with their 1-*N*- and 2-*N*-methyl derivatives suggested that the tetrazoles exist predominantly in the 1-H form. Both $^1H$ and $^{13}C$ n.m.r. spectra suggested the presence of interannular conjugation in 5-aryl-2-methyltetrazoles and 5-aryl-1*H*-tetrazoles. This was either reduced or absent in 5-aryl-1-methyltetrazoles and also in 5-(*o*-nitrophenyl)-1*H*-tetrazole.

THE tetrazole 5-C chemical shift differs significantly in 1,5- and 2,5-disubstituted tetrazoles,[1,2] and this difference is general for a wide range of 5-substituents.[3] Comparisons of tetrazole 5-C shifts with those of 1-*N*-methyl (I; R′ = Me) and 2-*N*-methyl (II; R′ = Me) isomers therefore can be used to monitor tetrazole annular tautomerism.[1,3] This approach requires the assumption that the 5-C shift is independent of exocyclic σ bonds and we have commented [3] on this previously. Since there is only one C atom in the tetrazole ring, the tautomerism can be approximately † quantified by a simple expression $\delta = N_1\delta_1 + N_2\delta_2$ in which $\delta$ is the measured 5-C shift and $N_1$ and $N_2$ represent the mole fraction of the 1-H and 2-H tautomers and $\delta_1$ and $\delta_2$ the 5-C shifts of the 1-N-Me and 2-N-Me isomers respectively.[3,‡,§]

† The use of the chemical shifts of *N*-Me isomers in place of the chemical shifts of the corresponding *N*-H tautomers is an obvious approximation and the conclusions are subject to its reliability. With other tetrazoles similar results were obtained when *N*-Bz and *N*-Me isomers were used as models (ref. 3) and this supports the assumption that the 5-C shift is not greatly influenced by exocyclic σ bonds. The approach of using *N*-alkylated isomers as models for *N*-H tautomers has been used widely for studies involving parameters such as $^1H$ n.m.r., u.v. spectra, dipole moments, $^{13}C$ n.m.r., basic p$K_a$ values, $^{14}N$ n.m.r. (a review, ref. 4). Such an approach is necessary since measurements cannot be made on the individual tetrazole tautomers. The value of the approach is supported by the general consistency of the results despite some discrepancies. In the case of tetrazole itself the agreement of the results using $^{13}C$ n.m.r. and $^1H$ n.m.r. (where the 5-H shift is independent of the nature of the ring *N*-substituent) also supports the models (ref. 1). Proton n.m.r., however, cannot be used as a double check with 5-substituted tetrazoles. With the present 5-aryltetrazoles the agreement of the $^1H$ n.m.r. data for interannular conjugation with the $^{13}C$ data for annular tautomerism further supports the method. Precise values (Table 1), measured within the experimental error, are quoted from the data on *N*-Me models, but variations of as much as 5% of the tautomerism could be involved (ref. 3).

‡ That such a 1-NH conformation should be preferred for compound (12) seems unexpected since, presumably, it is less stable than a 2-NH form possessing interannular conjugation. However, molecular models suggest that for an angle of *ca.* 40° between the rings a non-linear N–H · · · O, intramolecular hydrogen bond could be formed between the 1-NH and the *o*-$NO_2$ group and thus provide a source of stabilisation.

§ *Note added in proof.* In view of the carbon shifts it was of interest to enquire whether the acid-strengthening *ortho*-substituent effects of benzoic acids are present in substituted 5-phenyltetrazoles. The following acidic p$K_a$ values (±0.1) (average of five titrations; spread per titration, 0.1) were determined by potentiometric titrations in water at the temperatures shown, 5-phenyltetrazole, 4.32 (25 °C); 5-(*p*-nitrophenyl)-tetrazole, 3.25 (70 °C); 5-(*o*-nitrophenyl)tetrazole, 3.30 (25 °C); benzoic acid standard, 4.25 (25 °C). These and other acidity measurements will be discussed elsewhere.

[1] J. Elguero, C. Marzin, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 357.

[2] A. Konnecke, E. Lipmann, and E. Kleinpeter, *Tetrahedron*, 1976, **32**, 499.

[3] R. N. Butler and T. M. McEvoy, *Proc. Roy. Irish Acad.*, (RIC Centenary Issue), 1977, in the press.

[4] R. N. Butler, *Adv. Heterocyclic Chem.*, (*a*) 1977, **21**, pp. 355—359; (*b*) p. 328.

Because of the increasing interest [4a,5-7] in replacing the $-CO_2H$ group of biologically active molecules with the tetrazole group $CN_4H$, a knowledge of the influence of the tetrazole 5-substituent on the annular tautomerism is particularly desirable. For the 5-substituents, $NH_2$, Me, and Cl we have previously [3] obtained the respective 1-H : 2H tautomer percent ratios of 93 : 7, 55 : 45, and 48 : 52 using this $^{13}C$ n.m.r. method. In the present work we have examined the influence of some 5-aryl substituents. A previous preliminary attempt to study the tautomerism of a 5-aryltetrazole by $^{15}N$–$^1H$ coupling proved unsuccessful.[8]

## RESULTS AND DISCUSSION

(a) *Annular Tautomerism.*—The carbon chemical shifts of a series of 5-aryltetrazoles measured in dimethyl sulphoxide–water (83 : 17 v/v) as solvent are given in Table 1. In each case the 5-C-shifts suggest that the 1*H*-tautomer (I; R′ = H) predominates. The tautomerism was not greatly influenced by substituents in the phenyl ring but the $NO_2$ group seemed to orient the tautomerism towards the 2-H form (II) to a significant degree. The similarity between the *ortho*- and *para*-$NO_2$ groups [compounds (9) and (12)] suggests that the effect of the *ortho*-$NO_2$ group is mainly electronic and the steric factor may be negated by rotation of the tetrazole ring as in structure (IV; H for Me).

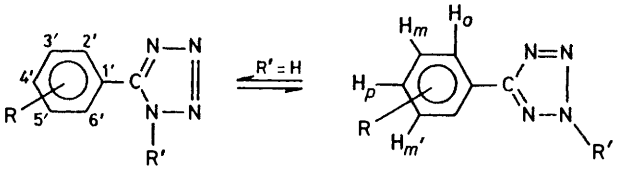
There has been no previous discussion of annular tautomerism of 5-aryltetrazoles but it has been tacitly assumed that the 2-H form predominates. In most papers in which a 5-phenyltetrazole is drawn, it is generally the 2-H form that is represented. The origin of this assumption appears to be data such as u.v. spectra and proton n.m.r. phenyl shifts (*e.g.* Table 2) where the spectra of the parent ring-unsubstituted tetrazole is generally closer to the 2-methyl isomer than to the 1-methyl form. However, such data are strongly governed by interannular conjugation and they do not mean that the 2*H*-tautomer is indicated but rather that there is considerable interannular conjugation in 5-aryl-1*H*-tetrazoles. This is not surprising since there is strong interannular conjugation in 2-phenylimidazole [9] which, like 5-aryltetrazoles, contains the PhC(=N–)–NH moiety.

TABLE 1

Carbon n.m.r. shifts (p.p.m. from $SiMe_4$) [a]

| Compound no. | 5-C | (I)/(II) | C-1′ | C-2′ | C-3′ | Δ [g] | C-4′ |
|---|---|---|---|---|---|---|---|
| (1) | 154.1 | | 120.45 | 128.5 | 129.8 | 1.3 | 141.45 |
| (2) [b] | 164.3 | | 124.15 | 126.25 | 129.95 | 3.7 | 140.47 |
| (3) | 155.3 | 88 : 12 | 120.85 | 126.8 | 129.95 | 3.15 | 141.55 |
| (4) | 154.2 | | 123.25 | 128.6 | 129.3 | 0.7 | 131.37 |
| (5) | 164.25 | | 126.7 | 126.4 | 129.3 | 2.9 | 130.7 |
| (6) | 155.6 | 86 : 14 | 123.8 | 127.1 | 129.5 | 2.4 | 131.6 |
| (7) [c] | 152.7 | | 129.9 | 130.25 | 124.0 | −6.25 | 148.85 |
| (8) [c] | 162.5 | | 132.7 | 127.5 | 124.4 | −3.1 | 148.45 |
| (9) | 155.8 | 68 : 32 | 130.73 | 128.25 | 124.5 | −3.7 | 148.8 |
| (10) [d,h] | 151.95 | | 118.65 | 133.1 | 134.6 | −1.5 | 132.3 |
| (11) [e,h] | 160.7 | | 120.1 | 130.8 | 133.1 | −2.3 | 131.9 |
| (12) [f] | 153.9 | 78 : 22 | 119.15 | 131.5 | 133.9 | −2.4 | 132.4 |

[a] Measured in $Me_2SO$–$H_2O$ (83 : 17, v/v) unless stated otherwise. [b] Measured in $Me_2SO$–$H_2O$ (86 : 14 v/v). [c] Measured in $Me_2SO$. [d] C-5′, 125.45; C-6′, 147.8. [e] C-5′, 124.2; C-6′, 148.6. [f] C-5′, 124.8; C-6′, 148.1. [g] C-3′ minus C-2′. [h] Measured in $Me_2SO$–$H_2O$ (89 : 11 v/v).



(I) (II)

(1) R = *p*-Me, R′ = Me
(3) R = *p*-Me, R′ = H
(4) R = H, R′ = Me
(6) R = H, R′ = H
(7) R = *p*-$NO_2$, R′ = Me
(9) R = *p*-$NO_2$, R′ = H
(10) R = 6′-$NO_2$, R′ = Me
(12) R = 6′-$NO_2$, R′ = H

(2) R = *p*-Me, R′ = Me
(5) R = H, R′ = Me
(8) R = *p*-$NO_2$, R′ = Me
(11) R = 6′-$NO_2$, R′ = Me

TABLE 2

Proton n.m.r. shifts (τ values)

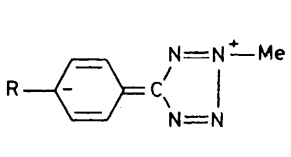
| Compound no. | $H_o$ | $H_m$ | $\Delta H_m$ [d] | *N*-Me |
|---|---|---|---|---|
| (1) | 2.36 | 2.66 | | 5.84 |
| (2) | 2.00 | 2.76 | +0.10 | 5.66 |
| (3) | 2.00 | 2.64 | | |
| (4) [a] | 2.36 | 2.36 | | 5.84 |
| (5) [a] | 1.87 | 2.59 | +0.23 | 5.75 |
| (6) [a] | 1.90 | 2.49 | | |
| (7) [a] | 1.95 | 1.44 | | 5.75 |
| (8) [a] | 1.79 | 1.79 | +0.35 | 5.58 |
| (9) | 1.63 | 1.63 | | |
| (10) | $H_{o,m,p}$, 2.08—2.24 | $H_{m'}$, 1.63—1.72 [e] | | 6.06 |
| (11) | $H_m$, $H_p$, 2.24—2.36 [b] | $H_o$, $H_{m'}$, 2.0—2.16 [c] | +0.40 [f] | 5.56 |
| (12) | $H_{o,m,p}$, 2.10—2.30 | $H_{m'}$, 1.84—1.92 [e] | | |

[a] Similar $^1H$ n.m.r. shifts have been reported, ref. 10. [b] Overlapping signal for Hs *meta* to both the tetrazole ring and the $NO_2$ group (2 H). [c] Overlapping signal for H's *ortho* to both the tetrazole ring and the $NO_2$ group (2 H). [d] $H_m$ for structure (II) minus $H_m$ for structure (I). [e] Multiplet due to ABCD pattern (1 H). [f] $H_{m'}$ differences for structures (II) and (I).

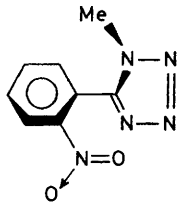
[5] J. S. Morley, *J. Chem. Soc.* (*C*), 1969, 809.
[6] Z. Grzonka and B. Lieberek, *Tetrahedron*, 1971, **27**, 1783; and other papers of series.
[7] R. T. Buckler, *J. Medicin. Chem.*, 1972, **15**, 578.
[8] P. Scheiner and J. F. Dinda, *Tetrahedron*, 1970, **26**, 2619.
[9] M. Begtrup, *Acta Chem. Scand.*, 1973, **27**, 3101.

The 5-C shifts appear to provide a more reliable probe of the tautomerism because the differences for the two isomeric models are not influenced by interannular conjugation since they are consistent, both in magnitude and direction, with cases where the 5-substituent has no conjugation with the tetrazole ring.[3] The similarity in the aromatic region of the proton spectra of 5-(*o*-nitrophenyl)tetrazole (12) with that of the 1-methyl isomer (10) (Table 2) contrasts with the other cases and supports the suggestion of out-of-plane rotation of the tetrazole ring giving a preferred conformation in which the 1*H*-form dominates.‡

(b) *Interannular Conjugation.*—Proton n.m.r. shifts for the series of 5-aryltetrazoles are summarised in Table 2. For the compounds (1)—(9), the *ortho*-protons were deshielded and the *meta*- and *para*-protons shielded in the 2-methyl isomer relative to the 1-methyl isomer. This is due to interannular conjugation in the 2-methyl case which is absent in the 1-methyl case.[10,11] The progressive increase in the shielding of the *meta*-protons for compounds (2), (5), (8), and (11) (Table 2; $\Delta H_m$) suggests a major contribution to the interannular conjugation from a form such as (III) whose importance is increased by electron-withdrawing substituents on the




(III)




(IV)

phenyl ring and diminished by electron-donating substituents. Fraser and Haque [10] have previously suggested an electron-donating resonance interaction in these systems. The *ortho*-nitrophenyl series (10)—(12) is interesting since the aromatic shifts for the parent compound (12) and the 1-methyl-isomer (10) were similar suggesting little difference in interannular conjugation. This may be reduced in both cases due to out-of-plane rotation of the tetrazole ring.‡ In the case of 1-methyl-5-(*o*-nitrophenyl)tetrazole (10) the plane of the tetrazole ring may be perpendicular to the plane of the phenyl ring, (IV), to reduce the steric interactions. Thus in this compound the 1-*N*-Me protons are exceptionally shielded having the largest shielding shift relative to the 2-*N*-Me group for any tetrazole system. [Table 2, compare *N*-Me shielding for the pairs (1), (2); (4), (5); (7), (8); and (10), (11]. These protons also have the second highest shielding reported among 1-methyltetrazole derivatives (the highest being $\tau$ 6.18 for 5-amino-1-methyltetrazole [4b]). This suggests that these Me protons encroach on the shielding region of the phenyl $\pi$-cloud above the plane of the phenyl ring, *e.g.* structure (IV).

‡ See note on p. 1087

[10] R. R. Fraser and K. E. Haque, *Canad. J. Chem.*, 1968, **46**, 2855.

[11] R. N. Butler, *Canad. J. Chem.*, 1973, **51**, 2315.

The carbon n.m.r. data (Table 1) also show the interannular conjugation in the differences between the C-3′ and C-2′ shifts ($\Delta$).[9] When $\Delta$ is large, 2.9—3.7 p.p.m., there is interannular conjugation. When $\Delta$ is smaller, 0.7—*ca.* 1.4, this conjugation is generally reduced or absent. These limits are more diffuse than those previously suggested [9] for tetrazoles on the basis of the two compounds (4) and (5) only and proton n.m.r. seems to be superior for studying this phenomenon in 5-aryltetrazoles. For example, with compound (6) the proton data strongly indicate conjugation whereas carbon data, with $\delta$(C-3′) — $\delta$(C-2′) = 2.4, are indecisive. The parameter $\delta$(C-3′) — $\delta$(C-2′) is confusing when the phenyl groups contain strongly interacting substituents, *e.g.* compounds (7) *vs.* (8) and (10) *vs.* (11). For the full series $\delta$(C-3′) varied very little between structures (I) and (II) while $\delta$(C-2′) was shifted upfield significantly in structure (II). The consistency of the data is more obvious if the parameter $\delta$(C-2′) for (I) minus $\delta$(C-2′) for (II) is considered, *i.e.* (1) *vs.* (2), 2.25; (4) *vs.* (5), 2.2; (7) *vs.* (8), 2.75; and (10) *vs.* (11), 2.3 p.p.m. Hence conjugation results in an upfield shift of $\delta$(C-2′) by 2.2—2.75 p.p.m. and little change in $\delta$(C-3′). This shift in $\delta$(C-2′), although small, is significant and it was both interesting, and surprising, that both the $^1$H and $^{13}$C data suggested considerable interannular conjugation in 2-methyl-5-(*o*-nitrophenyl)tetrazole (11). Molecular models confirmed that little or no twisting of the tetrazole ring or the *o*-$NO_2$ group was necessary in this compound. However, introduction of a proton or a methyl group at the 1-*N* position required a considerable twist to avoid a strong steric interaction with the *o*-$NO_2$ group and this was in agreement with the n.m.r. data for compounds (10) and (12) which indicated reduction or loss of conjugation. Table 1 shows that C-4′ is slightly shielded by interannular conjugation but the C-1′ signal is deshielded by 2.8—3.7 p.p.m. in the 2-*N*-Me isomers relative to the 1-*N*-Me derivatives (except for the *ortho*-nitrophenyl case where the deshielding is smaller). The carbon data on the parent compounds (3), (6), (9), and (12) (see Table 1) suggest that the C-1′ shift is strongly influenced by the tautomeric bonding structure of the tetrazole ring since for these compounds the phenyl C-1′ shifts parallel the tetrazole C-5 shifts in being similar to those of the 1-*N*-Me tetrazole derivatives. Hence the difference in the C-1′ shifts for 1-*N*-Me and 2-*N*-Me isomers is probably due mainly to the nature of the bonded tetrazole tautomeric type rather than to interannular conjugation since the proton data (Table 2) suggest that such conjugation is present in these 1-*N*-H tetrazoles while the phenyl C-1′ shifts are similar to the 1-*N*-Me isomers where such conjugation is absent.

The general additivity of substituent effects [12] on the phenyl carbon shifts was retained throughout the series and the interannular conjugation caused shielding shifts

[12] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, London, 1972, p. 81.

in the order C-2′ > C-4′ > C-3′ consistent with an electron-donating conjugation effect.

## EXPERIMENTAL

$^{13}C$ Shifts (±0.2 p.p.m.) were measured at probe temperatures on a JEOL FX-60 spectrometer. In all cases the solutions were 0.33M in substrate. Minor changes in the water content of the solvent mixture (Table 1, footnotes) were necessary due to small variations in solubilities of the substrates. These changes did not influence the shifts and for the *N*-Me isomers the 5-C shifts showed variations of less than the experimental error when measured in $Me_2SO$ or the $Me_2SO$–$H_2O$ mixtures. $^1H$ N.m.r. spectra were measured in $CDCl_3$–$(CD_3)_2SO$ (*ca.* 2 : 1 v/v) mixtures at probe temperatures on a JEOL JNM-100 spectrometer using solutions containing 20—30 mg of substrate per ml.

The tetrazoles were prepared by literature [4] procedures. Structures were confirmed by microanalysis and the n.m.r. spectra. The 5-(o-*nitrophenyl*)*tetrazole* (12), m.p. 165—166 °C (from ethanol) (Found: C, 44.1; H, 2.6; N, 36.95. $C_7H_5N_5O_2$ requires C, 44.0; H, 2.6; N, 36.65%) was prepared by heating a mixture of *o*-nitrobenzonitrile (7.40 g), sodium azide (5.35 g), n-butanol (22 ml), and glacial acetic acid (5.9 ml) under reflux for 4 days. The mixture was then treated with water (45 ml), reduced to *ca.* half volume, cooled, and adjusted to pH 3 when compound (12) (94%) separated. Methylation by literature procedures [10] gave 5-(o-*nitrophenyl*)-2-N-*methyltetrazole* (11), m.p. 79—81 °C (from methanol) (70%) (Found: C, 46.8; H, 3.4; N, 34.5. $C_8H_7N_5O_2$ requires C, 46.9; H, 3.45; N, 34.1%) and 5-(o-*nitrophenyl*)-1-N-*methyltetrazole* (10), m.p. 57—60 °C (from aqueous alcohol) (21%) (Found: C, 46.75; H, 3.45; N, 34.7%).

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