JOC The Journal of Organic Chemistry

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Experimental and GIAO ^{15}N NMR Study of Substituent Effects in 1*H*-Tetrazoles

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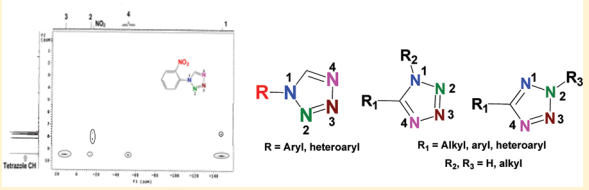
Supporting Information

ABSTRACT: A series of 1-aryl/alkyl-1*H*-1,2,3,4-tetrazoles, 5-substituted 1*H*-tetrazoles, and 1,5- and 2,5-disubstituted 1*H*-tetrazoles were studied by a combination of experimental NMR (natural abundance ^{15}N, ^{15}N/^{1}H HMBC, and ^{13}C) and computational GIAO-NMR techniques to explore substituent effects on ^{15}N (and ^{13}C) NMR chemical shifts in the tetrazole (TA) moiety. Computed ^{15}N chemical shifts via GIAO-B3LYP/6-311+G(2d,p) calculations gave satisfactory results in comparison with experimental data. Whereas N-alkylation leads to large ^{15}N chemical shift changes, changes in the N_1-aryl derivatives bearing diverse substituent(s) are generally small except for polar *ortho*-substituents (COOH, NO_2). Large $\Delta\delta^{15}$N values were computed in N_1-aryl derivatives for *p*-COH_2^+ and *p*-$OMeH^+$ as extreme examples of electron-withdrawing substituents on a TA moiety.



As a highly versatile functional group, the tetrazole (TA) moiety has found wide application in organic, organometallic, and medicinal chemistry.[1] With a high nitrogen content and low molecular weight along with favorable kinetic and thermal stability, the TA core has evolved into an important building block in high energy chemistry.[2] There has been extensive recent activity in the literature on the synthesis of TA-based energetic materials as potential replacements for common secondary explosives, and to this end a large number of energetic derivatives bearing nitro, nitroamino, nitroimino, and azido groups have been synthesized, with 5-aminotetrazole serving as a starting point.[3a−h] In some cases, these compounds served as precursors to ionic liquids (ILs),[3c,4c] and in other studies, energetic onium salts bearing the tetrazolate anion were synthesized and characterized.[4]

In the context of the aforementioned synthetic/preparative studies, ^{15}N NMR spectral data have been reported in some cases.[3,4] The ^{15}N NMR data on selected tetrazoles, tetrazolates, bis-tetrazolates, and mesoionic tetrazoles are available from earlier independent studies.[5] ^{15}N NMR was also employed to investigate tautomerism in certain substituted tetrazoles.[6] Although the available data could serve as a useful guiding tool, more systematic/comparative data are desirable to enable a more extensive substituent effect study. Given the ongoing current interest (also in other azoles[7]) as building blocks of energetic salts and ILs, and with the wide availability of natural abundance ^{15}N in combination with 2D-NMR, studies that are aimed at broadening its application in energetic materials as a potential diagnostic tool are warranted. In this juncture, the potential utility of computational ^{15}N GIAO (gauge-independent atomic orbitals) NMR studies to predict, with reasonable accuracy, the chemical shifts data for TA-based energetic ingredients becomes relevant.

We recently reported convenient high-yielding one-pot methods for the synthesis of 5-aryl-/alkyl-substituted 1*H*-tetrazoles[8a] and 1-aryl/alkyl-1*H*-tetrazoles[8b] and utilized these compounds as building blocks of heterocyclic systems and tetrazolium-ILs.[8] The tetrazolium salts were studied by ^{15}N NMR and by ^{1}H/^{15}N correlations.[8a] The availability of a series of 1-aryltetrazoles (**1**−**14**), 1-benzyltetrazole (**15**), the heterocyclic analogues (**16** and **17**), and a series of 5-aryltetrazoles (**18**−**23**) bearing a benzyl substituent at N_2 (**19**-**23**) together with the 1,5- and 2,5-dialkyl-TAs (**25**−**28**) (Figure 1) provided the impetus for the present study to gauge substituent effects transmitted via the ring nitrogen and carbon in the TA moiety on chemical shifts. In parallel, we explored the utility of ^{15}N GIAO-NMR to obtain computed chemical shifts for comparison with the experimental values.

Experimental and GIAO-NMR studies for compounds **1**−**17** are summarized in Table 1. Also included are the ^{13}C data for the ring carbon. Specific assignments were based on ^{15}N/^{1}H HMBC correlations for N_1 and N_3 with the TA ring C*H*. In the majority of cases (compounds **7**, **8**, **11**−**13**, **15**-**17**), HMBC correlations were also detected between phenyl C*H* (*ortho*) and N_1. The ^{15}N NMR spectra for compounds **11**, **12**, and **16** are shown in Figure 2 as representative cases.

NMR chemical shifts computed by GIAO-B3LYP/6-311+G-(2d,p) generally showed good agreement with the experimental data, with the closest match for N_1. The latter is consistently the most shielded nitrogen signal in the TA moiety, with the

Received: February 16, 2012
Published: April 5, 2012

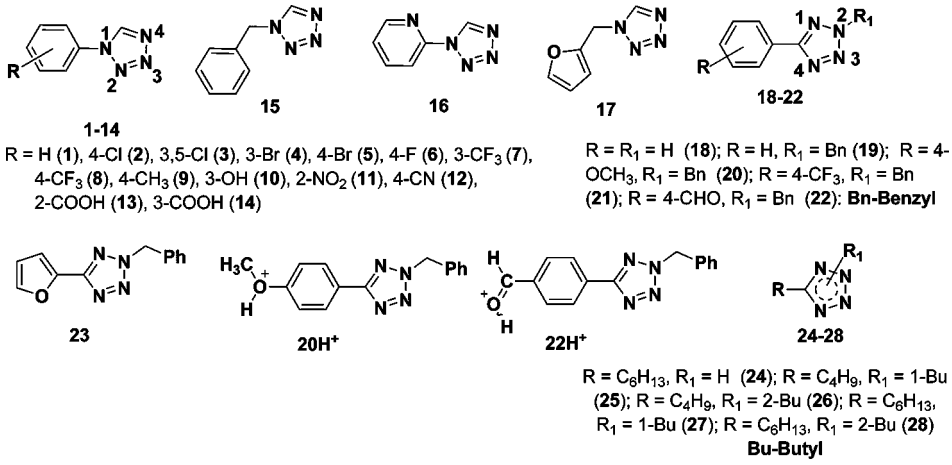


Figure 1. Compound sheet.

Table 1. Experimental and GIAO-B3LYP/6-311+G(2d,p) ^{15}N and ^{13}C NMR Data for 1-Substituted 1*H*-1,2,3,4-Tetrazoles (GIAO NMR-Derived Data in Parentheses)

compd	TA ring Carbon	N_1	N_2	N_3	N_4
1	140.7 (143.0)	−135.9 (−135.2)	−17.3 (−10.8)	11.3 (33.4)	−51.4 (−38.8)
2	140.6 (142.9)	−137.7 (−137.3)	−18.6 (−11.2)	11.7 (34.1)	no (−38.0)
3	140.5 (142.9)	−139.6 (−138.5)	−19.5 (−11.9)	12.5 (35.2)	−50.4 (−37.2)
4	140.6 (142.9)	−138.3 (−136.5)	−17.3 (−11.0)	12.7 (34.2)	no (−37.9)
5	140.5 (142.8)	−137.5 (−137.3)	−19.2 (−11.4)	11.9 (34.2)	no (−38.0)
6	140.8 (143.2)	−138.1 (−137.2)	−16.6 (−10.3)	12.1 (33.7)	no (−38.4)
7	140.6 (143.0)	−138.2 (−136.7)	−17.6 (−11.5)	12.6 (34.7)	−48.3 (−37.1)
8	140.6 (142.9)	−137.6 (−137.1)	−19.3 (−12.0)	12.6 (35.2)	−50.3 (−37.2)
9	140.6 (143.0)	−136.1 (−135.5)	−17.0 (−10.6)	11.3 (32.9)	no (−39.2)
10	140.6 (143.0)	−135.3 (−135.3)	−17.8 (−11.2)	10.8 (33.0)	no (−38.9)
11[a]	143.6 (150.4)	−148.1 (−150.1)	−13.8 (−3.5)	11.9 (31.0)	−52.3 (−45.4)
12[b]	140.8 (142.7)	−137.3 (−137.3)	−19.8 (−12.7)	12.9 (35.7)	−49.9 (−36.7)
13	144.1 (150.3)	−142.1 (−146.0)	−12.9 (−5.0)	9.1 (29.1)	−54.3 (−47.3)
14	140.8 (142.9)	−136.7 (−136.6)	−19.1 (−12.5)	11.8 (34.1)	−50.7 (−37.6)
15	142.5 (144.8)	−142.3 (−143.2)	−12.9 (−5.7)	10.8 (27.8)	no (−35.5)
16[c]	140.2 (144.4)	−130.2 (−131.4)	−21.1 (−4.2)	13.9 (32.5)	−50.5 (−40.4)
17	142.4 (144.8)	−144.9 (−147.6)	−13.7 (−7.7)	11.4 (30.9)	−51.7 (−37.5)

[a] −16.3 (−7.1) (NO_2). [b] −121.1 (−106.6) (CN). [c] −95.5 (−71.8) (N of pyridine). For compounds **1**, **4**, **6**, **7**, **9**, **15**, and **17**, $CDCl_3$ was used as NMR solvent while for the rest of the compounds $CDCl_3$ + DMSO-d_6 (1:1) was used; ^{15}N NMR spectra for compounds **1**−**3**, **8**, **10**, **12**, **13**, **15**, and **16** were recorded at 75% solution, while for rest of the compounds 60% solutions were used; no = not observed.

observed shielding order $N_1 \gg N_4 > N_2 > N_3$. It is noteworthy that GIAO-M062X/6-311+G(2d,p) calculations performed in representative cases in this study generally gave poor correspondence with experiments. We also carried out test calculations at the GIAO-B3LYP/aug-cc-pVDZ level, as this basis set was recently reported to perform well for some 5-amino- and 5-nitrotetrazoles,[9] but found no improvement. On this basis, our computational study focused only on GIAO-B3LYP/6-311+G(2d,p) computations.

Focusing on compounds **15** and **17**, strong HMBC correlation between the methylene C*H*$_2$ and N_1 was detected for both compounds. Except for N_3 that is deshielded, other TA nitrogens in **17** are more shielded relative to **15**, while the C*H* remains practically unchanged.

The NMR data for 1-aryltetrazoles generally show limited sensitivity to *para* and *meta* substituents even at N_1, irrespective of the nature of the substituent, but relatively large effects are observed (deduced from both GIAO-NMR and experimental values) with the *ortho*-substituted analogues **11** and **13**, exhibiting (relative to **1**) notable shielding of N_1, N_3, and N_4 and deshielding at N_2, with concomitant CH deshielding. The comparative data seem to indicate that transmission of substituent effect via N_1 is most sensitive to proximal rather than distal polar/inductive and mesomeric effects.

Experimental and GIAO-NMR data for the 5-aryltetrazoles (**18**−**23**) are summarized in Table 2. In the *N*-benzyl derivatives, HMBC correlations were detected between C*H*$_2$ and N_1 as well as with proximal N_2 and N_3 (not with N_4). N-Benzylation causes significant downfield shifts at N_2 and N_1 (**18** versus **19**). In comparing the data for the dialkyl-TA derivatives (**25**−**28**), butylation at N_1 (**25**, **27**) leads to strong shielding at that nitrogen with concomitant deshielding of N_2 and N_3 and shielding at CH. Similarly butylation at N_2 (**26**, **28**) causes strong shielding at N_2 and strong deshielding at N_1 and N_3. The HMBC correlations observed in **25** and **26** are sketched in Figure 3.

Focusing on the substituted 5-aryl derivatives, whereas small chemical shift changes are clearly detectable as a function of the *para* substituent, these electronic effects are not large enough to be diagnostic. To probe the limits of substituent effects on the

dx.doi.org/10.1021/jo300242s | *J. Org. Chem.* 2012, 77, 4152−4155

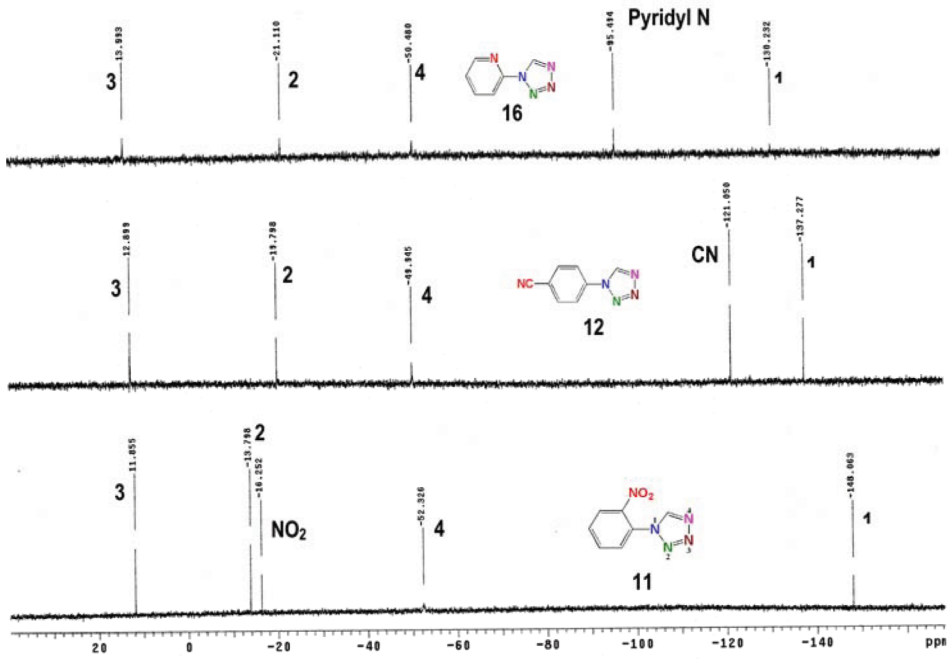


Figure 2. ^{15}N NMR spectra for **11**, **12**, and **16** in $CDCl_3$ + DMSO-d_6 (1:1).

Table 2. Experimental and GIAO-B3LYP/6-311+G(2d,p) ^{15}N and ^{13}C NMR Data for 5-Substituted 1*H*-Tetrazoles (GIAO NMR-Derived Data in Parentheses)

compd	TA ring carbon	N_1	N_2	N_3	N_4
18	155.8 (171.3)	−103.9 (−93.3)	no (−123.8)	−8.1 (6.4)	no (−46.2)
19	165.6 (171.9)	−84.8 (−87.5)	−95.9 (−92.6)	−1.1 (6.9)	−55.3 (−47.7)
20	165.5 (172.1)	−87.2 (−91.1)	−96.8 (−94.4)	−1.8 (6.3)	−57.2 (−49.6)
20H$^+$	(166.2) (−5.9[a])	(−77.0) (14.1[a])	(−80.3) (14.1[a])	(16.4) (10.1[a])	(−42.0) (7.6[a])
21	164.4 (170.9)	−82.8 (−84.9)	−94.4 (−90.9)	0.02 (8.6)	−53.7 (−45.8)
22	164.5 (171.1)	−81.6 (−83.4)	−93.6 (−90.4)	0.4 (8.7)	−52.8 (−44.3)
22H$^+$	(166.8) (−4.3[a])	(−56.8) (26.6[a])	(−70.2) (20.2[a])	(24.0) (15.3[a])	(−20.5) (23.8[a])
23	158.7 (165.3)	−87.4 (−89.4)	−96.1 (−93.5)	−1.5 (6.0)	−58.0 (−48.8)
24	157.1 (173.0)	no (−87.8)	no (−125.1)	−8.9 (8.4)	no (−39.3)
25	154.9 (159.8)	−147.0 (−152.7)	−12.5 (−7.8)	7.5 (29.5)	−55.8 (−45.3)
26	166.9 (174.1)	−81.7 (−81.6)	−96.5 (−95.2)	−1.7 (9.3)	−51.2 (−41.8)
27	154.8 (160.0)	−147.2 (−152.7)	−12.7 (−7.4)	7.1 (30.0)	−56.2 (−45.4)
28[b]	166.9 (174.3)	−80.9 (−82.5)	−96.2 (−96.9)	−0.5 (10.2)	−49.7 (−41.7)

[a] $\Delta\delta$ GIAO NMR values: cation minus neutral. [b] Neat; [at 75% solution in $CDCl_3$: −80.9 (N1), −96.0 (N2), −0.8 (N3), −50.9 (N4); at 50% solution in $CDCl_3$: −81.9 (N1), −96.7 (N2), −2.2 (N3), −52.5 (N4); at 25% solution in $CDCl_3$: −82.1 (N1), −96.5 (N2), 2.5 (N3), −52.9 (N4)]; $CDCl_3$ was used as NMR solvent for all compounds except for **18** and **22** for which CD_3CN + DMSO- d_6 (1:1) and DMSO-d_6 + $CDCl_3$ (1:4) were used respectively; ^{15}N NMR spectra for compounds **18** and **19** were recorded at 75% solution while **20**, **21**, and **28** were neat samples. Compounds **22**−**27** were used in 50% solution; no = not observed.

TA moiety, GIAO-NMR chemical shifts were computed for oxonium ion **20H$^+$** and carboxonium ion **22H$^+$**. This led to notable deshielding of the ring nitrogens and shielding at CH, consistent with extended charge delocalization and tetrazolium ion character. The magnitude of $\Delta\delta$ values in **20H$^+$** and **22H$^+$** and comparison with other cases (for example **19** versus **21**) (Table 2) imply that extended resonance delocalization is more effective than inductive withdrawal.

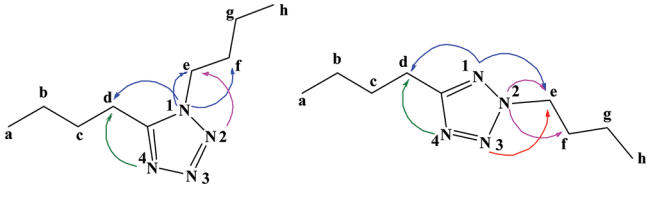


Figure 3. HMBC correlations in **25** and **26**.

SUMMARY

In summary, the TA core in 1-aryl-1*H*-tetrazoles appears to be minimally influenced by the inductive and mesomeric effects of remote substituent(s); only with *ortho*-substituted analogues **11** and **13** were notable chemical shift changes observed. With the 5-aryl/alkyl derivatives, whereas N-substitution has a major effect on the nitrogen chemical shifts, substantially less influence is observed by substitutions in the aryl ring. Only in extreme cases, with oxonium and carboxonium ion substituents, were notable chemical shift changes detected

dx.doi.org/10.1021/jo300242s | J. Org. Chem. 2012, 77, 4152−4155

that imply extended mesomeric and inductive effects. GIAO-B3LYP/6-311+G(2d,p) does a reasonably good job in predicting the NMR shifts in the TA core, with the ring carbon and N_1 showing closest correspondence with experiment in the 1-aryl derivatives.

EXPERIMENTAL SECTION

The tetrazoles used in this study were available from our previous work,[8] and their analytical and spectral data had been reported.

^{15}N NMR spectra were recorded on a 500 MHz instrument (^{1}H: 499.843 MHz; ^{15}N: 50.653 MHz) using a 5 mm AutoX Broadband probe with *z*-gradient. The typical parameters for 1D ^{15}N experiment were: spectral width 20 kHz; acquisition time 0.8s; 45° pulse for excitation; relaxation delay 5s; and temperature 25 °C. The number of scans was set according to the sample concentration. The typical number was 9500 (15 h). Some of them were 40000 (64 h). The ^{15}N NMR spectra were externally referenced relative to neat $MeNO_2$ (0 ppm), without using coaxial capillary tubes. For 2D gradient selected $^{1}H-^{15}N$ HMBC experiments, the spectral widths of ^{1}H and ^{15}N dimensions were adjusted according to 1D ^{1}H and ^{15}N spectrum, respectively. Typically, 16 scans were acquired for each t1 increment with the total 128 increments. The acquisition times were 150 ms on F2 (^{1}H), and 12 to 23 ms (max) on F1 (^{15}N) dimension. The relaxation time was 1s. The data was processed with zero-filling on F1 and F2 dimension, linear prediction on F1 dimension, and window functions of squared sinebell on F2 and Gaussian on F1 before Fourier Transform.

Computational Details. Calculations were performed with the Gaussian 09 suite of programs.[10] Structures were fully optimized by density functional theory (DFT) with the B3LYP[11] functional and the 6-311+G(2d,p) basis set. All computed geometries were verified to be minima by harmonic vibrational frequency calculations (no imaginary frequencies). NMR chemical shifts were calculated by the GIAO (gauge independent atomic orbitals)[12] method at the B3LYP/6-311+G(2d,p) level and in selected cases also by GIAO-M062X[13]/6-311+G(2d,p) and by GIAO-B3LYP/aug-cc-pVDZ computations.

The ^{13}C and ^{15}N NMR chemical shifts were referenced to TMS and CH_3NO_2 respectively (GIAO magnetic shielding tensors were 182.5 ppm for ^{13}C in TMS, and −153.2 ppm for ^{15}N in nitromethane; these values are related to the GIAO isotropic magnetic susceptibility).

ASSOCIATED CONTENT

Supporting Information

^{15}N and $^{1}H-^{15}N$ HMBC spectra and tables of Cartesian coordinates for compounds **1**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the University of North Florida for support. G.L.B. acknowledges financial support from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and the Secretaría de Ciencia y Tecnología de la Universidad Nacional de Córdoba (Secyt-UNC).

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