Research Article

Magnetic Resonance in Chemistry

Received: 3 April 2011 Revised: 28 May 2011 Accepted: 2 June 2011 Published online in Wiley Online Library: 5 August 2011

(wileyonlinelibrary.com) DOI 10.1002/mrc.2790

Isotopic effect on tautomeric behavior of 5-(2,6-disubstituted-aryloxy)-tetrazoles

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Isotopic effect on tautomeric behaviors of the synthesized 5-phenoxy- (1a), 5-(2,6-dimethylphenoxy)- (1b), 5-(2,6-diisopropylphenoxy)- (1c), 5-(2,6-dimethoxyphenoxy)- (1d) and 5-(4-methylphenoxy)-tetrazole (1e) were investigated in DMSO-d_6 by adding one drop of D_2O. Among 1a–e, 1a, 1d and 1e show small rotational barrier around C5–O1 and O1–C6 while in 1b and 1c there are distinguishable rotational barrier about that bonds. The ^{1}H NMR spectra of 1b and 1c show slightly different chemical shifts for two methyl and isopropyl groups on those phenyl ring, respectively, while the chemical shifts difference ($\Delta\delta$) between two methyl and two isopropyl groups were enhanced by adding D_2O. The ^{13}C NMR spectra of 1b show two overlapped singlets for methyl groups after adding D_2O. Representatively, the calculations of compound 1c were performed with GAUSSIAN-03and the rotational barrier about C5–O1 and between isopropyl group and phenyl ring in 1c was calculated with B3LYP/6-31G(d) basis set.

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; rotational barrier; isotope effect; tautomeric behavior; 5-aryloxy tetrazole

Introduction

5-Substituted tetrazoles are reported to possess antibacterial,[1–3] antifungal,[4] antiviral,[5–7] analgesic,[8–11] anti-inflammatory,[12–15] antiulcer[16–18] and antihypertensive[19,20] activities. The tetrazole function is metabolically stable.[21,22] This feature and a close similarity between the acidic character of the tetrazole group and carboxylic acid group[23–25] have inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents. Tetrazoles are an increasingly important functionality, not only as precursors to a variety of nitrogen-containing heterocycles[26] but also as materials with applications in explosives[27] and even as increasive lubricants.[28]

Several works were reported about tetrazole tautomerization[29–34] and isomerization.[35,36] But as part of investigations of 5-(2,6-disubstituted-aryloxy)-tetrazoles, there is no report about isotope effect on tautomerization of these compounds. We report herein the protium/deuterium isotope effect on tautomeric behavior of these compounds in DMSO as suitable solvent with adding one drop of D_2O.

Experimental

Instruments and materials

Compounds **1a–e** were dissolved in DMSO-d_6 (99.8%) and deuteration was achieved by the addition of a drop of D_2O (99.95%). The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 FT-NMR spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) in DMSO-d_6 at ambient temperature (26 °C) using 5 mm direct detection broadband probes and deuterium lock. The center of the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 2.49 ppm (^{1}H) and δ 39.5 ppm (^{13}C). The ^{1}H signal of DOH appeared at δ 3.99 ppm (variable).

The recording conditions were the following: ^{1}H NMR: pulse width (90°) = 8.2 μs, acq. time = 2.65 s, digital resolution = 0.19 Hz/data point, d1 = 1 s, td = 32768, ns = 16, experimental time = 64 s, spectral width = 6172.8 Hz, dw = 81 μs, de = 6 μs; ^{13}C NMR: pulse width (90°) = 6.3 μs, acq. time = 1.82 s, digital resolution = 0.27 Hz/data point, d1 = 2 s, td = 65536, ns = 1200, experimental time = 4800 s, spectral width = 17985.6 Hz, dw = 27.8 μs, de = 6 μs.

Syntheses

Tetrazoles **1a–e** were synthesized based on reported literatures by the reaction of phenol and its derivatives with cyanogen bromide and subsequently 1,3-dipolar cycloaddition reaction with sodium azide then acidified with HCl (37%).[29,30] All Attempts was failed in results for the synthesis of tetrazoles **1f** and **1g** in similar manner based on reported literatures.[29,30]

Computational details

Representatively, the calculations of compound **1c** were performed with GAUSSIAN-03 packages.[37] Molecular geometries was calculated at DFT (B3LYP)[38–40] at 6-31G(d) basis set.

Results and Discussion

This paper presents results on the tautomeric behavior of 5-aryloxy-tetrazole derivatives (**1a–e**) via deuteration of exchangeable proton on those tetrazole rings. Tetrazole ring can exist in two tautomeric forms of (1*H*)- and (2*H*)-tetrazole in polar and nonpolar

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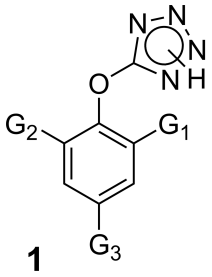


$G_1 = G_2 = G_3 =$ H (**a**)
$G_1 = G_2 = CH_3$, G_3 = H (**b**)
$G_1 = G_2 = CH(CH_3)_2$, G_3 = H (**c**)
$G_1 = G_2 = OCH_3$, G_3 = H (**d**)
$G_1 = G_2$ = H, $G_3 = CH_3$ (**e**)
$G_1 = C(CH_3)_3$, $G_2 = G_3$ = H (**f**)
$G_1 = G_2 = C(CH_3)_3$, G_3 = H (**g**)

Figure 1. The general formula structures of tetrazoles **1a–g**.

solvents, respectively.[29] The general formula structure of 5-aryloxy-tetrazoles **1** that studied in this work, are shown in Fig. 1.

5-Substituted tetrazoles are existed as equilibrium mixtures of those 1*H*- and 2*H*-tautomers.[29] Buttler[32] discussed the rapid equilibrium of 5-substituted 1*H*- and 2*H*-tetrazoles. Dabbagh and Lwowski reported[29] that ^{15}N NMR spectra of 5-methoxytetrazole indicate only two signals (rapid equilibrium) at δ −19.0 and at −126.0 ppm corresponding to N=N and N–H, respectively. The proton on tetrazole ring is delocalized due to fast tautomerization on N1 and N2 atoms.

The ^{1}H and ^{13}C NMR spectra of 5-(2,6-dimethylphenoxy)-(1*H*)-tetrazole (**1b**) shows interesting phenomenon before and after adding D_2O while 5-phenoxy-(1*H*)-tetrazole (**1a**) do not. Before adding D_2O, two methyl groups upon phenyl ring in **1b** show a singlet at δ 2.09 ppm and have a shoulder in the peak's right side while these methyl groups show two distinct peaks at δ 2.064 and 2.050 ppm after adding D_2O ($\Delta\delta$ = 0.014 ppm; Fig. 2). The appearance of a shoulder in the peak's right side can attribute to slightly nonequivalency of methyl groups upon phenyl ring in **1bA** tautomer (tetrazole-H) before adding D_2O (in comparison with **1e** that showed a singlet for methyl group on *para*-position). This observation indicated the equilibrium mixture of two tautomers **1bA** and **1bB** (fast equilibrium) and two methyl groups having equivalent chemical shift in **1bB** (2*H*-tetrazole-H), slightly nonequivalent in **1bA** tautomer (1*H*-tetrazole-H), respectively (Fig. 2(a)). After adding D_2O, two methyl groups became slightly nonequivalent in **1bB** (2*H*-tetrazole-D) and obviously nonequivalent in **1bA** (1*H*-tetrazole-D), respectively (Fig. 2(b)). The rotational barrier increased around C5–O1 and also O1–C6 bonds due to substitution of deuterium on tetrazole ring (Fig. 2(b) and Scheme 1(a)). Generally, deuteration on tetrazole ring is fast and our aim for partial deuteration of tetrazole ring were unsuccessful. Therefore two methyl groups have different chemical shift on phenyl ring moiety where N1 atom was deuterated (**1bA** form). Nonequivalency of the chemical shifts of two methyl groups on **1bA** corresponds to the slightly restriction of the rotation

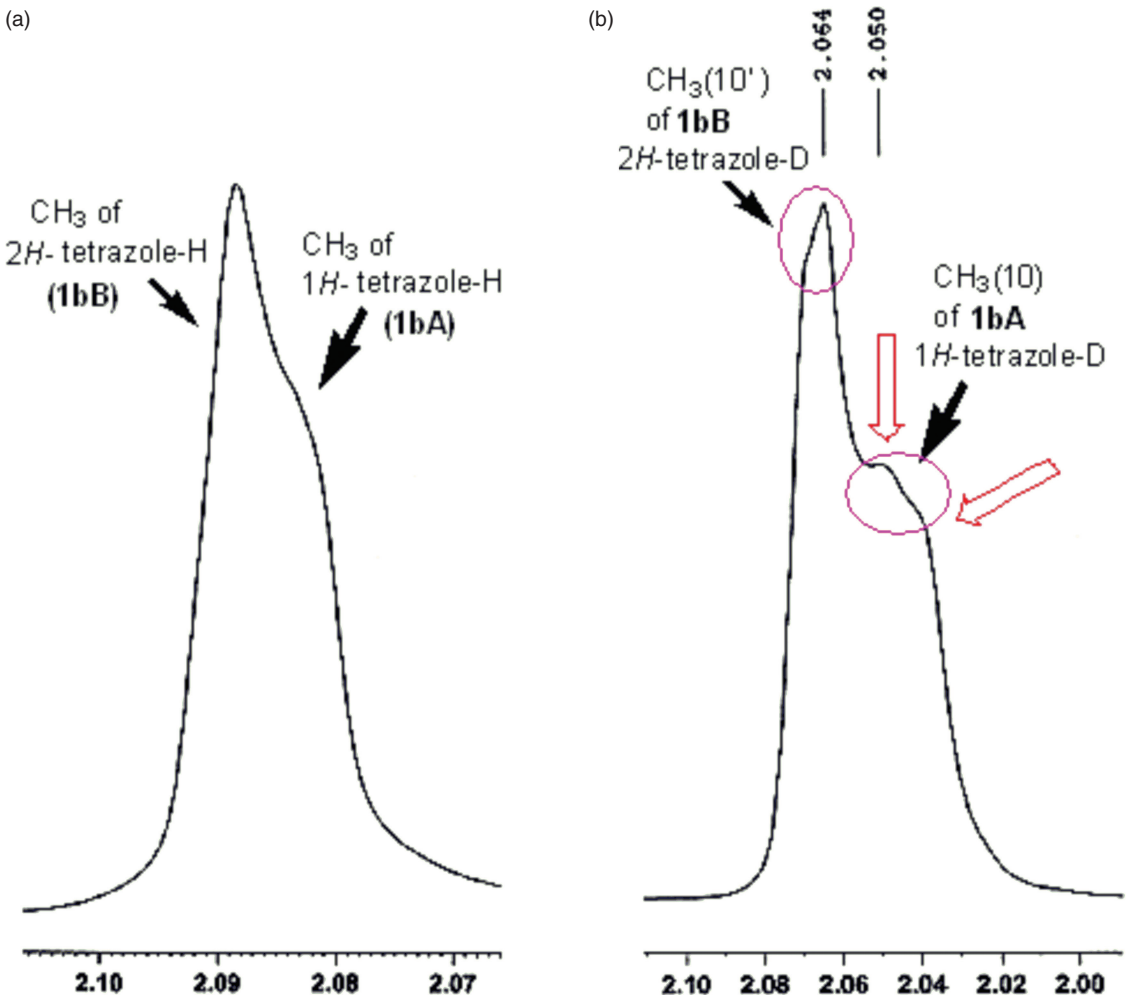
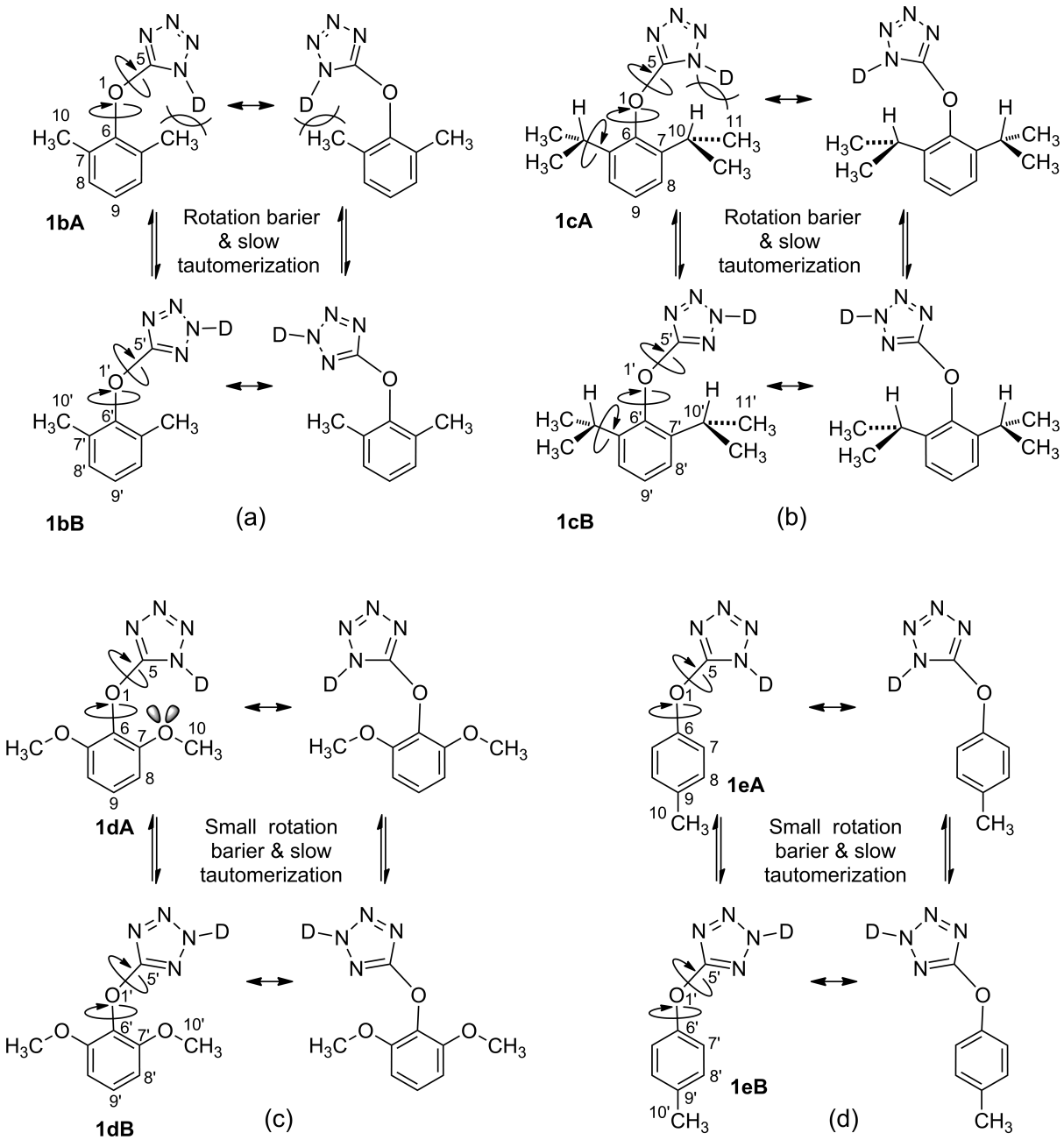


Figure 2. Expanded ^{1}H NMR spectra of methyl group of **1b** before (a) and after adding D_2O (b) in DMSO-d_6.



Scheme 1. Comparison of the rotational barrier in deuterated tetrazoles **1bA** (a), **1cA** (b), **1dA** (c) and **1eA** (d).

around the ether linkage between tetrazole and phenyl ring bearing methyl groups on *ortho*-positions (Fig. 2(b) and Scheme 1(a)). The covalent bond length of N–D is longer than that of N–H bond (d_{N-H} = 0.80 Å vs d_{N-D} = 1.01 Å)[41] and caused to increasing the rotational barrier of tetrazole ring around C5–O1 and also O1–C6 bonds (ether linkage bond). In ^{13}C NMR spectrum of **1b**, before adding D_2O, the chemical shifts of two methyl groups are equivalent at δ 16.07 ppm while after adding D_2O, the chemical shifts of those methyl groups are slightly nonequivalent (at δ 15.98 ppm and has a shoulder in the peak's right side; Fig. 3).

In **1b**, the substitution of deuterium on tetrazole ring also restricted the rapid tautomerization (Scheme 1a) and thus, the equilibrium mixture of **1bA** and **1bB** were existed in solution after adding D_2O. The methyl groups show two peaks, a slightly broadened singlet at δ 2.064 and two overlapped peaks at 2.050 ppm (Fig. 2(b)). It seems that this peak at δ 2.064 ppm corresponds to deuterated 2*H*-tetrazole tautomer **1bB** (2*H*-tetrazole-D) form in which two methyls have chemical shift equivalent. The substitution of deuterium on N2 atom upon tetrazole ring has no steric effect to the methyl groups (lower than that of 1*H*-tetrazole-D). Two overlapped peaks at 2.050 ppm corresponds to methyl groups with different chemical shift on phenyl ring in deuterated 1*H*-tetrazole tautomer **1bA** due to steric repulsion between deuterium and methyl groups. This observation confirms that the equilibrium mixture of two deuterated 1*H*- and 2*H*-tetrazoles have enough life time in NMR time scale, approximately (Fig. 2). Quantitatively determination of

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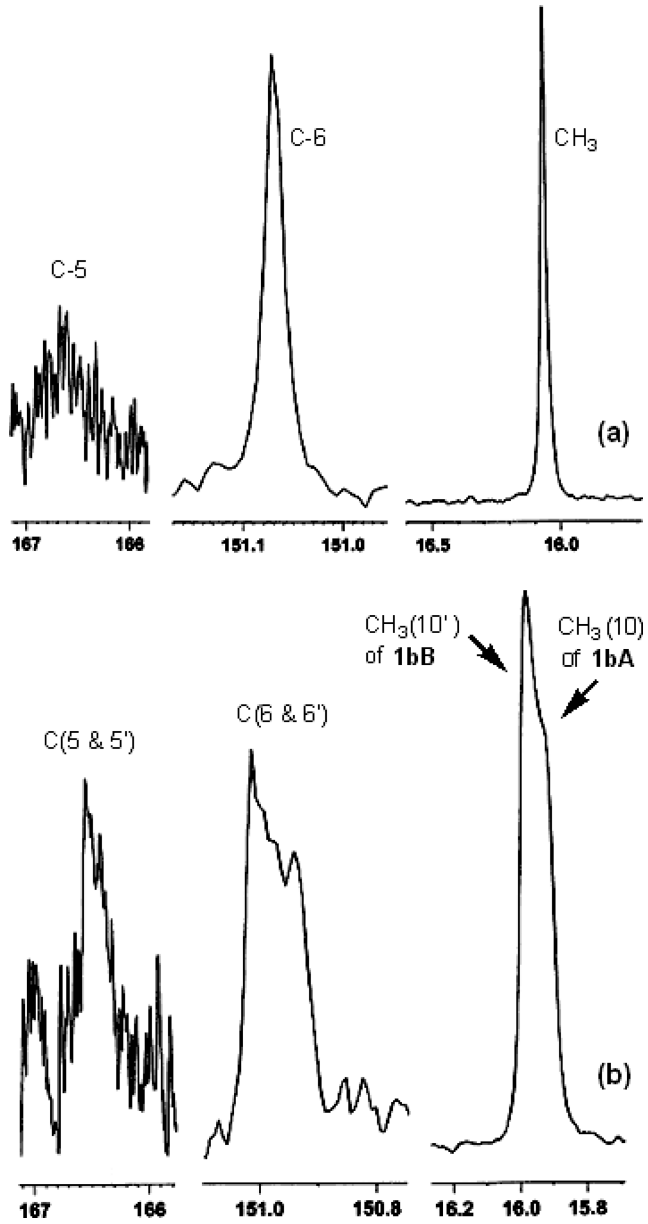

Figure 3. Expanded ^{13}C NMR spectra of **1b** before (a) and after adding D_2O (b) in DMSO-d_6.

each tautomers in equilibrium mixtures of **1bA** and **1bB** is difficult because of the peak overlapping.

In ^{13}C NMR spectrum of deuterated **1b**, the *ipso*-carbon atom on phenyl ring (bonded to O1) show two peaks at δ 151.01 and at ≈150.94 ppm correspond to C6 and C6′ in equilibrium mixture of **1bA** and **1bB** forms (Fig. 3(b) and Scheme 1(a)). The carbon atom of tetrazole ring (C5) show a multiplet and can attributed to equilibrium mixture of **1bA** and **1bB** (C5 and C5′). There is no probability of β-isotope effect in 1*H*-tetrazole-D tautomer because of no partial deuteration of this tautomer (full deuteration and no formation of isotopomers). Of course, several works have been reported about protium/deuterium β- and γ-isotope effects in ^{13}C NMR spectroscopy of other organic compounds, e.g. carbohydrates, amines, ammonium salts, amino acids,[42–50] amides,[51–55] barbiturate azo dyes[56] and also β-isotope effect and tautomeric forms of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and

Table 1. Chemical shifts of carbon atoms in tetrazoles **1a–e** before and after adding D_2O[a]

Atom	1a	1b	1c	1d	1e
C5[b]	166.80	166.60	167.70	C	166.84
d	166.69	166.50	167.62	C	166.80
C6	154.59	151.07	148.47	152.36	152.46
	154.39	151.01	148.39	152.31	152.34
C7	119.41	130.14	140.44	131.40	119.30
	119.41	130.11	140.40	131.31	119.31
C8	130.48	129.57	125.02	127.37	130.73
	130.55	129.58	125.03	127.46	130.77
C9	126.01	126.78	127.52	105.90	135.26
	126.20	126.86	127.61	105.88	135.43
C10	–	16.07	27.11	56.52	20.73
		15.98[e]	27.09	56.50[f]	20.68
C11	–	–	23.42	–	–
			23.34[f]		

[a] One drop of D_2O was added.
[b] The chemical shift(s) before adding D_2O.
[c] The peak intensity was low and unclear.
[d] The chemical shift(s) after adding D_2O.
[e] The peak has a shoulder in the peak's right side.
[f] The peak has a shoulder in the peak's left side.

their sulfur analogs.[57] The ^{13}C NMR data of **1a–e** are summarized in Table 1 before and after adding D_2O.

From **1b** to **1c** the rotational barrier was enhanced with substitution of the bulky substituent of isopropyl at *ortho* position in **1c**. The ^1H NMR analyses of 5-(2,6-diisopropylphenoxy)-tetrazole **1c** proved that the phenyl ring bearing two isopropyl groups are forced to lie out of the plane of the tetrazole due to the steric hindrance exerted by the presence of two isopropyl groups. This conformation was clearly deduced by the X-ray crystallographic analysis and calculation of **1c** (Fig. 4). Before adding D_2O, Fig. 5(a) show a doublet and having a shoulder at the peak's right side and indicates the two isopropyl groups are slightly nonequivalent on phenyl ring. After adding D_2O, the ^1H NMR spectrum shows two environments for isopropyl groups [δ 1.040 and 1.052 ppm in which two equal coupling constants (J = 6.3 Hz)], which can be ascribed to the frozen rotation about the aryl-oxygen bonds on the NMR time scale and equilibrium mixture of two tautomers (**1cA** and **1cB**) as shown in Fig. 5.

However, expectedly, the ^1H NMR spectrum of 5-(2,6-diisopropylphenoxy)-tetrazole **1c** must show only one doublet peak belonging to the methyl groups indicating that the NMR time scale rotation around the ether linkage is allowed or fast enough to be detected at room temperature. Therefore, there is no exactly one doublet for isopropyl groups before adding D_2O in **1c**. This may be attributed to the absence of a hydrogen atom on N2-position (in case of tetrazole) in the non-peripheral phenyl positions, which clearly exert an additional steric hindrance in case of **1c** and hence preventing rotation around the aryloxy bond. In addition, in the 1*H*-tautomer the steric hindrance is higher than that of 2*H*-tautomer and exerts the restricted rotation around the aryloxy bond. Before adding D_2O, the ^1H NMR spectrum of **1c** shows a doublet at δ 1.083 ppm (J = 6.3 Hz) and another overlapped doublet appeared as a shoulder at the peak's right side. The methine proton of isopropyl group shows an overlapped septet at δ 2.890 ppm (Fig. 5(a)). The ^{13}C NMR spectrum shows a peak at δ 23.42 and 27.12 ppm for methyl and methine carbons on isopropyl

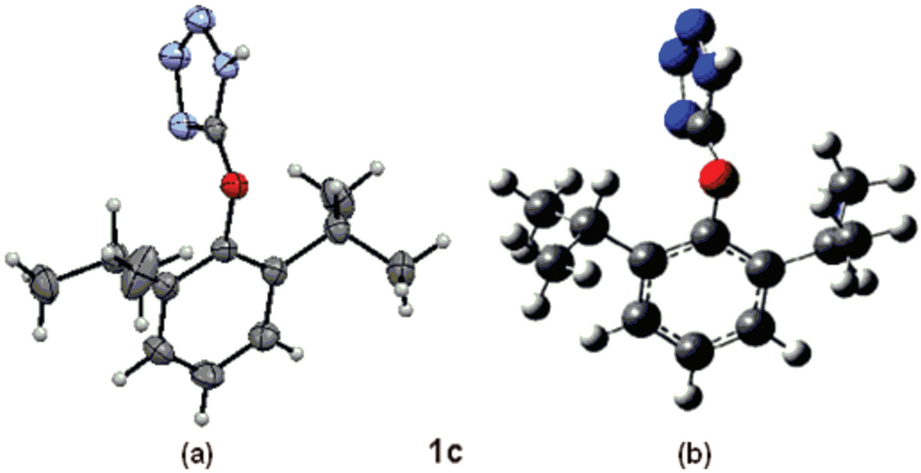

Figure 4. The crystal structure (a) and optimized structure of **1c** calculated at B3LYP/6-31G(d) level of theory (b).

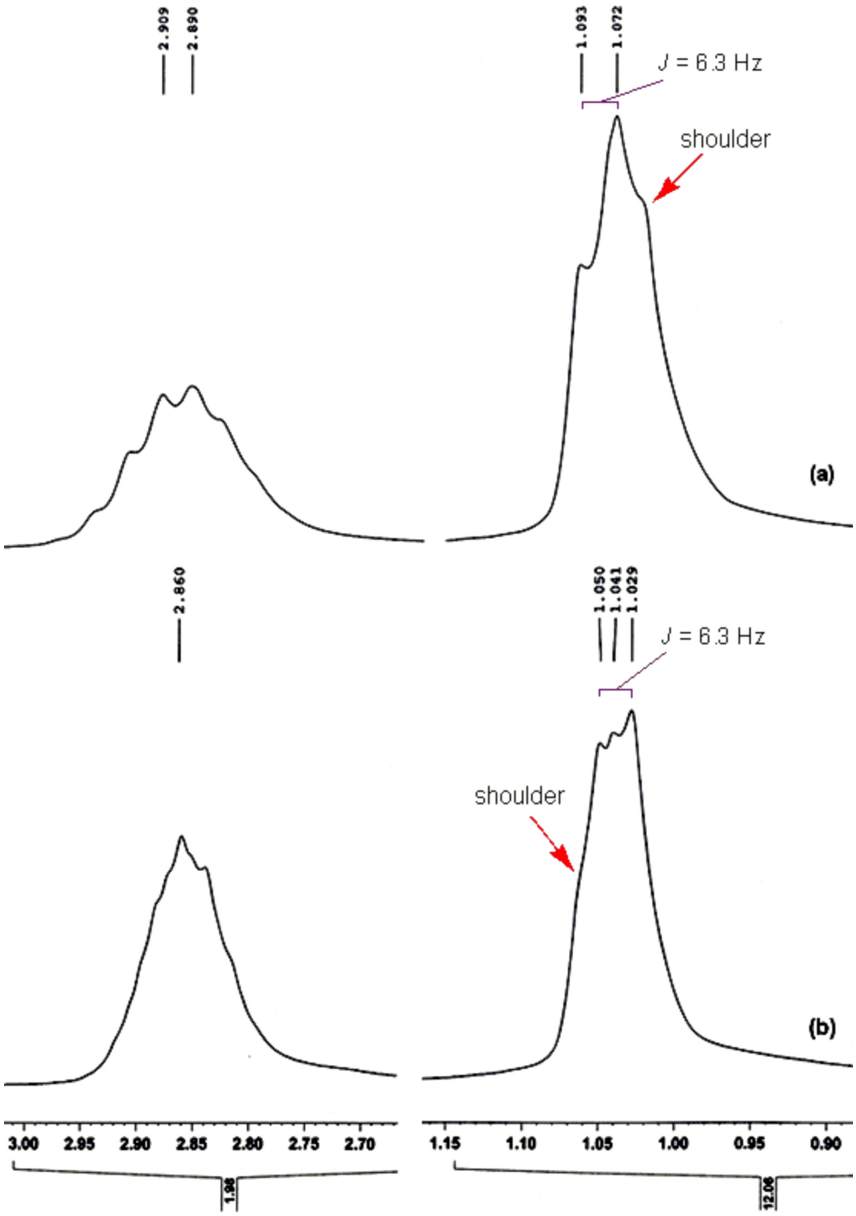

Figure 5. Expanded ^{1}H NMR spectra of isopropyl groups of **1c** before (a) and after adding D_2O (b) in DMSO-d_6.

groups, respectively. In contrast, after adding D_2O, the two isopropyl groups show obviously two overlapped doublets at δ 1.040 and 1.052 ppm with the same coupling constants (J = 6.3 Hz), respectively. The methine proton on isopropyl groups appeared as a multiplet that indicated minimum two overlapped septets (Fig. 5(b)). These observations revealed that slow tautomerization occurred and the equilibrium mixtures of two deutereted tautomers have enough life time in NMR time scale (Scheme 1(b) and Fig. 5(b)). Similar to **1b**, quantitatively determination of each tautomers in equilibrium mixtures of **1cA** and **1cB** is difficult because of the peak overlapping. This circumstance confirms the equilibrium mixtures of two 1*H*-tetrazole-D and 2*H*-tetrazole-D tautomers in **1c**.

For instance, two isopropyl groups in 2,6-diisopropylphenol (propofol, is a short-acting, intravenously administered hypnotic agent)[58] are equivalent in chemical shifts[59] because of the low rotational barrier. Therefore, it seems that the appearance of approximately two doublets in ^{1}H NMR spectrum of **1c** (before adding D_2O) either attributed to the hindrance effect between two isopropyls and tetrazole groups upon phenyl ring and restricted rotation around ether linkage bonds in **1c** or presumably to the equilibrium mixture of 1*H*- and 2*H*-tautomers that slightly have enough life time in NMR time scale. It seems that the hindrance effect of isopropyl groups is predominant. Presumably, two methyls upon isopropyl group are slightly nonequivalent in chemical shift because of the hindrance repulsion with tetrazole group and restriction of the rotation around the ether linkage bond and also rotation around the bond between isopropyl and phenyl ring (this case depends to temperature).

For further study about **1c**, the molecular geometry of compound **1c** was optimized by the calculation at DFT (B3LYP) at 6-31G(d) basis set (Fig. 4(b)). A rotational barrier around the bond between O1 and C5 was calculated and is shown in Fig. 6(a). The maximum and minimum energies calculated with B3LYP/6-31G(d) basis set derived from dihedral angles (φ) of 93° and 178° that equals to 7.36 and 0.00 kcal/mol, respectively (Fig. 6(a)). These energies were also calculated for rotational barrier between phenyl ring and isopropyl group (Fig. 6(b)). In the later case, the maximum and minimum energies for rotation around C7–C10 (between phenyl ring and isopropyl group) derived from dihedral angles (φ) of 158° and 64° that equals to 8.73 and 0.00 kcal/mol, respectively (Fig. 6(b)). These calculated results demonstrate that the rotational barrier around ether linkage bond is slightly lower than that of those between isopropyl group and phenyl ring (7.36 vs 8.73 kcal/mol).

For the further information and comparison with the calculated data, the crystal structure of **1c** is shown in Fig. 4(a). For the crystal structure determinations, single-crystals of **1c** were used for data collection on Oxford Diffraction Gemini E diffractometer. Measurements were made at 150 K with graphite monochromated Cu Kα radiation (λ = 1.54184 Å). The computing details; Data collection: Gemini, (Oxford Diffraction, 2006)[60]; cell refinement: *CrysAlis RED*, (Oxford Diffraction, 2002)[60]; data reduction: *CrysAlis RED*, (Oxford Diffraction, 2002)[60]; program(s) used to solve structure: *SIR92*[61]; program(s) used to refine structure: *CRYSTALS*[62]; molecular graphics: *CAMERON*[63] and software used to prepare material for publication: *CRYSTALS*.[62] The crystallographic data for structure **1** were deposited to the Cambridge Crystallographic Data Center (entry no. CCDC-819010) and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (Fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk).

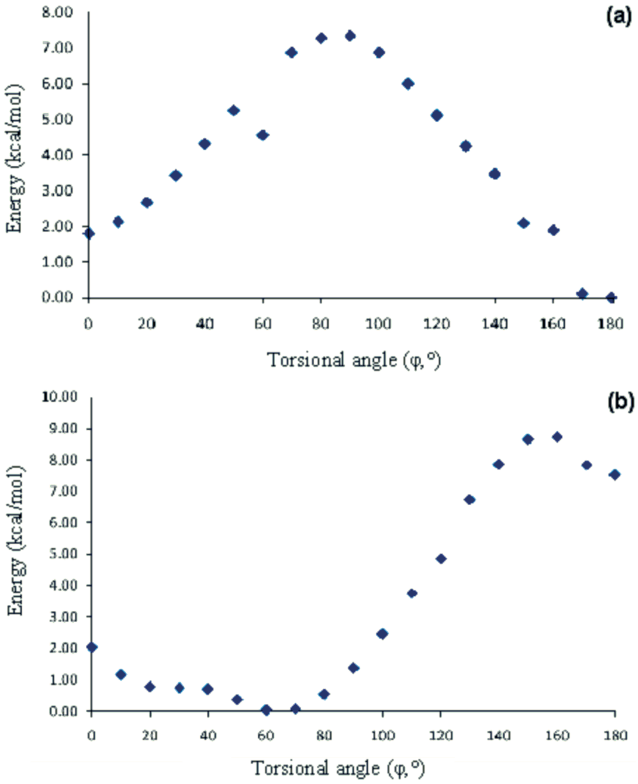

Figure 6. Diagram of rotational barriers around the bond between O1 and C5 (a) and between isopropyl group and phenyl ring (b) in optimized structure of **1c**. Calculated at B3LYP/6-31G(d) level of theory.

In contrast, in 5-(2,6-dimethoxyphenoxy)-tetrazole **1d**, the rotational barrier about C5–O1 and O1–C6 was lower than **1b** because of the less interaction of oxygen lone pairs with hydrogen and/or deuterium atom upon N1 of tetrazole ring (Scheme 1c). Before adding D_2O, the ^{1}H NMR spectrum of **1d** show a singlet for two methoxy groups and indicating two methoxy groups have chemical shift equivalent and each tautomer (**1dA** and **1 dB**) has no life time long enough in NMR time scale in equilibrium mixture (fast tautomerization). After adding D_2O, a shoulder at the peak's left side appeared for methoxy groups upon phenyl ring and indicated that two tautomers slightly having enough life time in NMR time scale, approximately (slow tautomerization; Fig. 7(A)).

We also performed the isotope effect experiment on 5-(4-methylphenoxy)-tetrazole **1e**. Similar to **1a, 1e** has no rotational barrier around O1–C5 and O1–C6 bonds (Table 1). On the other hand, the methyl group of **1e** shows a singlet at δ 2.295 and a broadened singlet δ 2.270 ppm (including a shoulder at the peak's left side) before and after adding D_2O, respectively (Fig. 7(B)). Similar to **1d**, especially in **1e**, the appearance of a shoulder in the peak's left side demonstrates the equilibrium mixture of two deuterated tautomers (**1eA** and **1eB**) that have enough life time in NMR time scale. This observation confirms the slow tautomerization of deuterated tetrazole ring (tetrazole-D) than that of tetrazole ring consisting of hydrogen atom (tetrazole-H).

Conclusion

In summary, the replacement of methyl, methoxy and isopropyl groups with hydrogen atom on *ortho* position of phenyl ring in deuterated 5-aryloxy tetrazoles restricted the rotation around

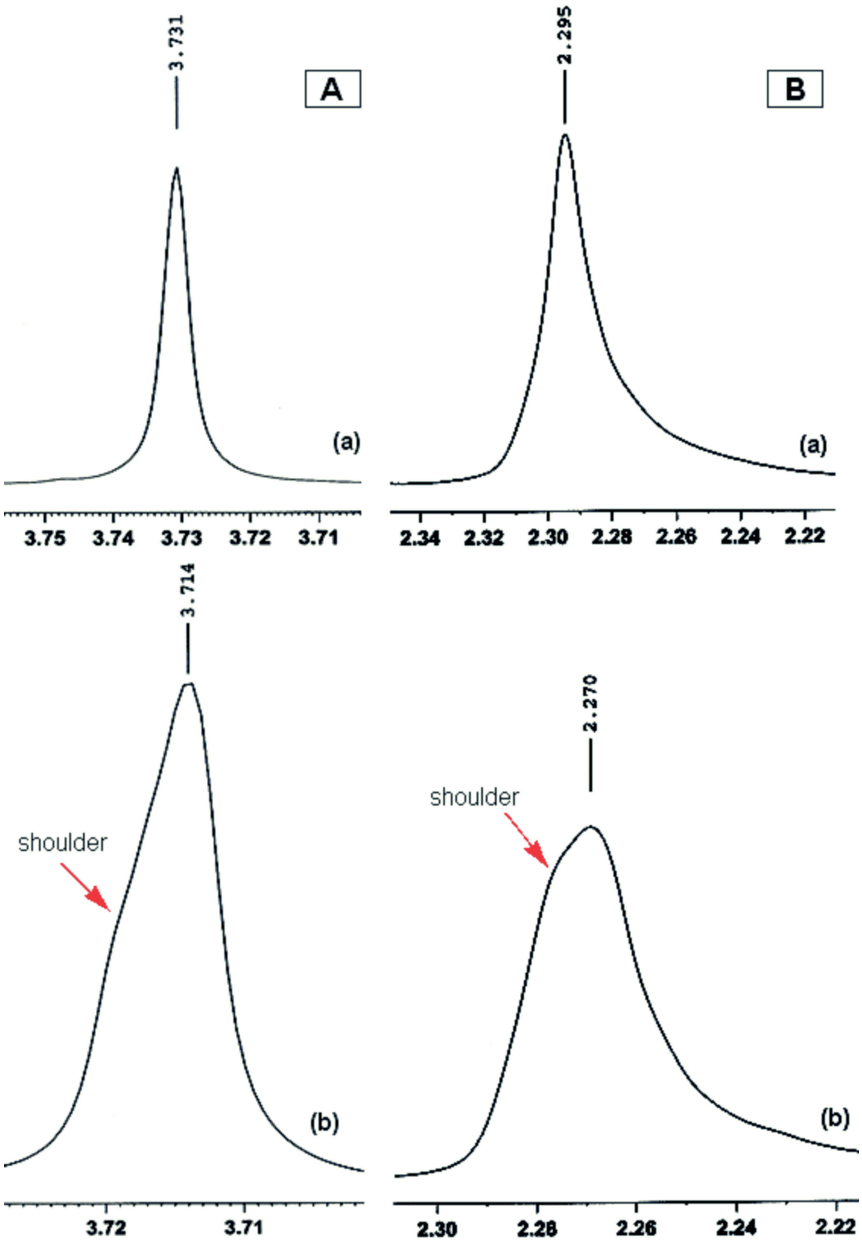

Figure 7. Expanded ^{1}H NMR spectra of methoxy group of **1d** (A) and methyl group of **1e** (B) before (a) and after adding D_2O (b) in DMSO-d_6.

C5–O1 and O1–C6 bonds. The substitution of deuterium on N1 atom upon tetrazole ring also restricted the mentioned above rotation due to N–D bond lengthening. Substitution of deuterium on tetrazole ring also slightly slowed down the tautomerization and caused each tautomers of 1*H*- and 2*H*-tetrazoles-D to have enough life time in NMR time scale in equilibrium mixture. The rotational barrier was enhanced by increasing the bulk of substituent on *ortho* position (from hydrogen to isopropyl). The rotational barrier was also slowed down by replacing methoxy with methyl group on *ortho* position upon phenyl ring.

Acknowledgements

The author thanks the Urmia University Research Council for supporting this work and also acknowledges gratefully to Mr S. Bavafa (from International University of Chabahar (IUC), Chabahar, Iran) for helping in calculating data and to X-ray crystallography lab of Universiti Putra Malaysia (UPM) for X-ray crystallographic data of compound **1c**.

Supporting information

Supporting information may be found in the online version of this article.

References

[1] Y. L. Janin, *Bioorg. Med. Chem.* **2007**, *15*, 2479.
[2] S. D. Diwakar, S. S. Bhagwat, M. S. Shingare, C. H. Gill, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4678.
[3] V. Åberg, P. Das, E. Chorell, M. Hedenstrm, J. S. Pinkner, S. J. Hultgren, F. Almqvist, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3536.

[4] R. S. Upadhayaya, N. Sinha, S. Jain, N. Kishore, R. Chandra, S. K. Arora, *Bioorg. Med. Chem.* **2004**, *12*, 2225.
[5] V. V. Zarubaev, E. L. Golod, P. M. Anfmov, A. A. Shtro, V. V. Saraev, A. S. Gavrilov, A. V. Logvinov, O. I. Kiselev, *Bioorg. Med. Chem.* **2010**, *18*, 839.
[6] R. Rönn, T. Gossas, Y. A. Sabnis, H. Daoud, E. Åkerblom, U. H. Danielson, A. Sandström, *Bioorg. Med. Chem.* **2007**, *15*, 4057.
[7] S. Malancona, S. Colarusso, J. M. Ontoria, A. Marchetti, M. Poma, I. Stansfeld, R. Laufer, A. D. Marco, M. Taliani, M. Verdirame, O. Gonzalez-Paz, V. G. Matassa, F. Narjes, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4575.
[8] K.-H. Lee, C.-E. Park, K.-H. Min, Y.-J. Shin, C.-M. Chung, H.-H. Kim, H.-J. Yoon, W. -Kim, E.-J. Ryu, Y.-J. Shin, H.-S. Nam, J.-W. Cho, H.-Y. Lee, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5567.
[9] J. R. Maxwell, D. A. Wasdahl, A. C. Wolfson, V. I. Stenberg, *J. Med. Chem.* **1984**, *27*, 1565.
[10] P. Kumar, E. E. Knaus, *Drug Des. Discov.* **1994**, *11*, 15.
[11] P. Vicini, L. Amoretti, E. Barocelli, M. Chiavarini, M. Impicciatore, *Farmaco* **1986**, *41*, 111.
[12] B. J. Al-Hourani, S. K. Sharma, J. Y. Mane, J. Tuszynski, V. Baracos, T. Kniess, M. Suresh, J. Pietzsch, F. Wuest, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1823.
[13] C. J. Shishoo, M. B. Devani, M. D. Karvekar, G. V. Vilas, S. Anantham, V. S. Bhaati, *Indian J. Chem.* **1982**, *21B*, 666.
[14] K. Pande, M. Tandon, T. N. Bhalla, S. S. Parmar, J. P. Barthwal, *Pharmacology* **1987**, *35*, 333.
[15] S. M. Ray, S. C. Lahiri, *Indian Chem. Soc.* **1990**, *67*, 324.
[16] M. Uchida, M. Komatsu, S. Morita, T. Kanbe, K. Yamasaki, K. Nakagawa, *Chem. Pharm. Bull.* **1989**, *37*, 958.
[17] I. Ueda, K. Ishii, K. Sinozaki, M. Hatanaka, *Chem. Pharm. Bull.* **1991**, *39*, 1430.
[18] K. Terashima, T. Tanimura, H. Shimamura, A. Kawase, K. Uenishi, Y. Tanaka, I. Kamisaki, Y. Ishizuka, M. Sato, *Chem. Pharm. Bull.* **1995**, *43*, 1042.
[19] J. Svetlik, L. Veizerová, T. U. Mayer, M. Catarinella, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4073.
[20] N. Kaur, A. Kaur, Y. Bansal, D. I. Shah, G. Bansal, M. Singh, *Bioorg. Med. Chem.* **2008**, *16*, 10210.
[21] H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul, R. K. Malhotra, *Prog. Med. Chem.* **1980**, *17*, 151.
[22] A. Palazzi, S. Stagni, S. Selva, M. Monari, *J. Organometall. Chem.* **2003**, *669*, 135.
[23] T. Kimura, Y. Hamada, M. Stochaj, H. Ikari, A. Nagamine, H. Abdel-Rahman, N. Igawa, K. Hidaka, J.-T. Nguyen, K. Saito, Y. Hayashi, Y. Kiso, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2380.
[24] T. Pinter, S. Jana, R. J. M. Courtemanche, F. Hof, *J. Org. Chem.* (In press); DOI: 10.1021/jo200031u.
[25] R. J. Herr, *Bioorg. Med. Chem.* **2002**, *10*, 3379.
[26] D. Moderhack, *J. Prakt. Chem.* **1988**, *340*, 687.
[27] M. Hiskey, D. E. Chavez, D. L. Naud, S. F. Son, H. L. Berghout, C. A. Bome, *Proc. Int. Pyrotech. Semin.* **2000**, *27*, 3.
[28] J. Li, T. Ren, H. Liu, D. Wang, W. Liu, *Wear* **2000**, *246*, 130.
[29] H. A. Dabbagh, W. Lwowski, *J. Org. Chem.* **2000**, *65*, 7284.
[30] H. A. Dabbagh, Y. Mansoori, *Russian J. Org. Chem.* **2001**, *37*, 1771.
[31] M. W. Wong, R. Leung-Toung, C. Wentrup, *J. Am. Chem. Soc.* **1993**, *115*, 2465.
[32] R. N. Butler, in *Comprehensive Heterocyclic Chemistry*, vol. 4, (Eds: A. R. Katritzky, C. W. Ress, E. F. V. Scriven), Pergamon: Oxford, **1996**, p 621.
[33] P. Cmoch, H. Korczak, L. Stefaniak1, G. A. Webb, *J. Phys. Org. Chem.* **1999**, *12*, 470.
[34] R. E. Trifonov, I. Alkorta, V. A. Ostrovskii, J. Elguero, *J. Mol. Struct. (Theochem.)* **2004**, *668*, 123.
[35] S. L. Deev, Z. O. Shenkarev, T. S. Shestakova, O. N. Chupakhin, V. L. Rusinov, A. S. Arseniev, *J. Org. Chem.* **2010**, *75*, 8487.
[36] T. Sasaki, M. Kanematsu, M. Murata, *Tetrahedron* **1971**, *27*, 5121.
[37] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03, Revision B.03*, Gaussian, Inc., Pittsburgh, PA, **2003**.
[38] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.
[39] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372.
[40] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.
[41] J. B. Yang, J. Lamsal, Q. Cai, W. J. James, W. B. Yelon, *Appl. Phys. Lett.* **2008**, *92*, 091916(1)–091916(3).
[42] H. K. Ladner, J. J. Led, D. M. Grant, *J. Magn. Reson.* **1975**, *20*, 530.
[43] P. E. Pfeffer, F. W. Parrish, J. Unruh, *Carbohydr. Res.* **1980**, *84*, 13.
[44] J. Reuben, *J. Am. Chem. Soc.* **1984**, *106*, 2461.
[45] J. Reuben, *J. Am. Chem. Soc.* **1985**, *107*, 1433.
[46] J. Reuben, *J. Am. Chem. Soc.* **1983**, *105*, 3711.
[47] J. C. Christofides, D. B. Davies, *J. Am. Chem. Soc.* **1983**, *105*, 5099.
[48] J. Reuben, *J. Am. Chem. Soc.* **1985**, *107*, 1756.
[49] M. Yashiro, S. Yano, S. Yoshikawa, *J. Am. Chem. Soc.* **1986**, *108*, 1096.
[50] Z. Majerski, M. ŽuaniŠ, B. Metelko, *J. Am. Chem. Soc.* **1985**, *107*, 1721.
[51] J. Feeney, P. Partington, G. C. K. Roberts, *J. Magn. Reson.* **1974**, *13*, 268.
[52] P. A. Newmark, J. R. Hill, *J. Magn. Reson.* **1976**, *21*, 1.
[53] G. E. Hawkes, E. W. Randall, W. E. Hull, D. Gattegno, F. Conti, *Biochemistry* **1978**, *17*, 3986.
[54] M. Ottiger, A. Bax, *J. Am. Chem. Soc.* **1997**, *119*, 8070.
[55] P. E. Hansen, A. Kolonicny, A. Lyčka, *Magn. Reson. Chem.* **1992**, *30*, 786.
[56] N. Noroozi Pesyan, *Magn. Reson. Chem.* **2009**, *47*, 953.
[57] M. Rimaz, N. Noroozi Pesyan, J. Khalafy, *Magn. Reson. Chem.* **2010**, *48*, 276.
[58] J. Helfenbein, C. Lartigue, E. Noirault, E. Azim, J. Legailliard, M. J. Galmier, J. C. Madelmont, *J. Med. Chem.* **2002**, *45*, 5806.
[59] K. I. Momot, P. W. Kuchel, B. E. Chapman, P. Deo, D. Whittaker, *Langmuir* **2003**, *19*, 2088.
[60] Oxford Diffraction Ltd. *CrysAlis CCD, CrysAlis RED and CrysAlis PRO*, Oxford Diffraction Ltd: Abingdon, **2006**.
[61] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435.
[62] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout, D. J. Watkin, *J. Appl. Cryst.* **2003**, *36*, 1487.
[63] D. J. Watkin, C. K. Prout, L. J. Pearce. *CAMERON*, Chemical Crystallography Laboratory: Oxford, **1996**.

