Tetrahedron Letters 49 (2008) 4213–4215

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A ^{15}N NMR study of tautomerism in dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate

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ARTICLE INFO

Article history:
Received 18 March 2008
Revised 20 April 2008
Accepted 30 April 2008
Available online 4 May 2008

Dedicated to Professor Dr. Jaroslav Holeček on the occasion of his 75th birthday

Keywords:
Dihydro-1,2,4,5-tetrazine
^{15}N NMR
$^{n}J(^{15}N,^{15}N)$
Tautomerism

ABSTRACT

Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate can exist either in 1,2- or 1,4-dihydro tautomeric forms. The ^{15}N NMR spectra of dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate were measured at the ^{15}N natural abundance level as well as in ^{15}N doubly labelled selectively and in ^{15}N completely labelled compounds (20% ^{15}N). The $J(^{15}N,^{15}N)$ value was determined in ^{15}N completely labelled compounds (20% ^{15}N) using 1D ^{15}N INADEQUATE and was found to be 12.2 ± 0.2 Hz in deuteriochloroform, acetonitrile-d_3, DMSO-d_6 and CD_3OH. Very similar ^{15}N chemical shifts and $^{1}J(^{15}N,^{1}H)$ values were also observed in all the solvents. This indicates that compound **1** exists completely in the 1,4-dihydro tautomeric form (i.e., as dimethyl 1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate) in all the solvents tested.

3,6-Disubstituted dihydro-1,2,4,5-tetrazines can exist either in 1,2- or in 1,4-dihydro tautomeric forms (Fig. 1).

Rau and Hu[1] performed an X-ray study of diethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate ($X = COOC_2H_5$) and found that in the solid state this compound exists as the 1,4-dihydro derivative, the six-membered ring having a boat conformation. The 1,4-dihydro tautomer exists preferentially in solutions,[2] however, both 1,2- and 1,4-dihydro tautomeric forms were mentioned in a recent paper[3] in which compounds with different substituents X were studied in hexadeuteriodimethyl sulfoxide solution. The authors determined ^{1}H, ^{13}C and ^{15}N chemical shifts as well as $^{n}J(^{13}C,^{1}H)$ and $^{n}J(^{15}N,^{1}H)$ coupling constants, however, the conclusions concerning tautomerism were somewhat ambiguous.

The spectral problem arises because both 1,2- and 1,4-dihydro tautomers are symmetrical molecules giving the same number and the same types of NMR signals. The tautomerism can be solved under these circumstances by comparison with suitable model compounds, prediction of chemical shifts or applying computational methods. However, there is no doubt that experimental methods, giving convincing and conclusive evidence about the tautomeric equilibrium, would also be desirable.

The aim of this Letter was to analyse the 1,2- versus 1,4-dihydro tautomerism (Fig. 2) in dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) using ^{15}N enriched substances in several solvents.

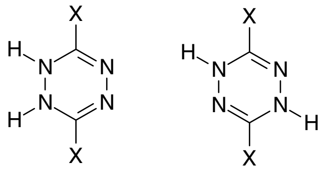

Figure 1. Formulae of 3,6-disubstituted 1,2- and 1,4-dihydro-1,2,4,5-tetrazines.

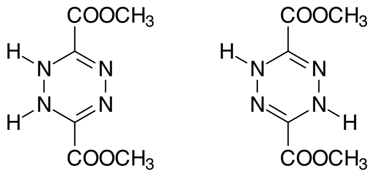

Figure 2. Formulae of dimethyl 1,2- and 1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylates.

Since the tautomeric changes occur at the nitrogen atoms, ^{15}N NMR spectroscopy should be an ideal tool to differentiate the forms. Palmas et al.[3] measured ^{15}N chemical shifts as well as $^{n}J(^{15}N,^{1}H)$ coupling constants at the natural abundance level of the ^{15}N nucleus in 3,6-disubstituted dihydro-1,2,4,5-tetrazines,

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doi:10.1016/j.tetlet.2008.04.161

however, the conclusions concerning tautomerism remained incompletely solved.

Therefore, we decided to use ^{15}N labelled compounds. First, we prepared (by a known method[4,5]) ^{15}N doubly labelled dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate using Na^{15}NO$_2$ (20% ^{15}N) and recorded NMR spectra. The ^{1}H and ^{15}N NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at 500.13 MHz and 50.68 MHz, respectively. The ^{15}N chemical shifts were referred to external neat nitromethane in a co-axial capillary ($\delta = 0.0$). The negative values of ^{15}N chemical shifts denote shifts of signals to lower frequencies with respect to the standard. We observed two ^{15}N resonances in the ^{15}N NMR spectrum of ^{15}N doubly labelled dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (Fig. 3).

This approach did not lead to a final conclusion. If no proton exchange occurred, only one ^{15}N resonance should be observed as is clear from structure **1a** (Fig. 4). Proton exchange can, however, follow either path A or path B, both leading to structures that would give two ^{15}N resonances in the ^{15}N NMR spectrum (two different nitrogens in compound **1b** and the equimolar equilibrium of forms **1a** and **1c**, see Fig. 4).

We realised that solving the problem required determination of the $^{n}J(^{15}N,^{15}N)$ coupling constants. Previously we succeeded in measuring $^{n}J(^{15}N,^{15}N)$ coupling constants in (^{15}N(enriched)–^{15}N(natural abundance)) pairs[6] provided the measured compound was very soluble. Unfortunately, the solubility of dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate is rather low (especially in CD$_3$CN and CD$_3$OH) and, thus, it was necessary to prepare completely ^{15}N labelled dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate[4,5] using Na^{15}NO$_2$ (20% ^{15}N) and (^{15}N)-glycine (20% ^{15}N) (Fig. 5).

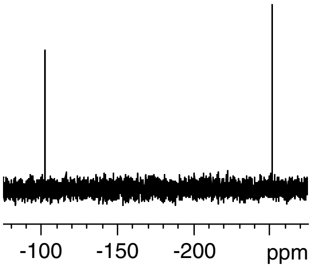

Figure 3. ^{15}N NMR spectrum of ^{15}N doubly labelled compound **1** in deuteriochloroform measured using inverse-gated decoupling (decoupler 'on' during acquisition time only).

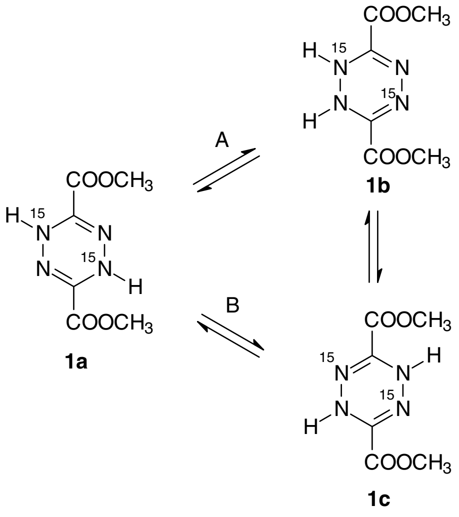

Figure 4. Possible proton transfer among ^{15}N doubly labelled forms **1a–c**.

1D ^{15}N INADEQUATE was optimised for $J(^{15}N,^{15}N) = 6$ and 12 Hz and the experimental digital resolution was 0.18 Hz/point. Compound **1** was dissolved in CDCl$_3$ (30 mg in 0.6 ml of solvent), CD$_3$CN (saturated solution), (CD$_3$)$_2$SO (25 mg in 0.6 ml of solvent), CD$_3$OH (saturated solution) and the spectra were recorded at 300 K. The ^{15}N chemical shifts and $^{1}J(^{15}N,^{1}H)$ and $J(^{15}N,^{15}N)$ coupling constants are collected in Table 1.

In all the solvents, we observed $J(^{15}N,^{15}N)$ coupling constants being 12.2 ± 0.2 Hz (Fig. 6). We believe that this J value belongs undoubtedly to a one-bond $J(^{15}N,^{15}N)$ coupling constant corresponding to an –NH–N= arrangement, that is, to dimethyl 1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate. We previously determined very similar $^{1}J(^{15}N,^{15}N)$ coupling constants in substituted azo compounds[7] (Ar^1–N=N–Ar^2) being ca. 15 Hz and in hydrazones[7] (Ar^1–NH–N=X) $^{1}J(^{15}N,^{15}N)$ being ca. 11 Hz. In contrast, much smaller two-bond $J(^{15}N,^{15}N)$ coupling constants would be expected if the structure of compound **1** corresponded to dimethyl 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate since it is known that $^{2}J(^{15}N,^{15}N)$ coupling constants are in the range 1–5 Hz.[8,9]

The NMR data in Table 1 show that dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) exists exclusively in the 1,4-dihydro tautomeric form in different solvents (low polar and aprotic CDCl$_3$, CD$_3$CN, polar and aprotic (CD$_3$)$_2$SO and polar and protic CD$_3$OH). Moreover, no difference was observed in the $^{1}J(^{15}N,^{1}H)$

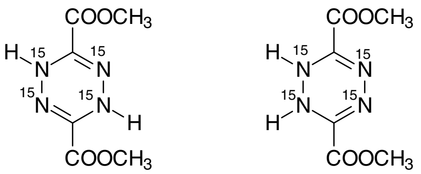

Figure 5. Formulae of completely ^{15}N labelled dimethyl 1,2- and 1,4-dihydro-1,2-,4,5-tetrazine-3,6-dicarboxylates.

Table 1
^{15}N chemical shifts and $^{1}J(^{15}N,^{1}H)$ and $^{1}J(^{15}N,^{15}N)$ coupling constants (Hz, ±0.2 Hz) of compound **1** in several solvents at 300 K

	CDCl$_3$	CD$_3$CN	(CD$_3$)$_2$SO	CD$_3$OH
$\delta(^{15}N)_{-N=}$	−102.8	−99.9	−98.6	−102.2
$\delta(^{15}N)_{-NH-}$	−251.4	−250.9	−249.2	−250.9
$\lvert ^{1}J(^{15}N,^{1}H)\rvert$	88.3[a]	89.0	90.0[a]	89.0
$\lvert ^{1}J(^{15}N,^{15}N)\rvert$	12.2	12.3	12.2	12.1

[a] The same value was observed at 330 K.

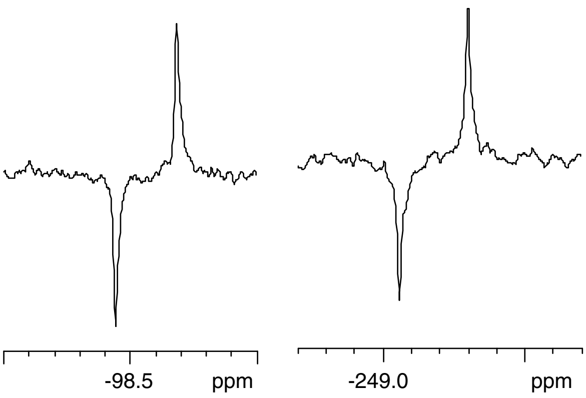

Figure 6. Parts of the 1D ^{15}N INADEQUATE spectrum of ^{15}N completely labelled compound **1** in hexadeuteriodimethyl sulfoxide optimised for $^{1}J(^{15}N,^{15}N) = 12$ Hz.

coupling constant values measured at 300 and 330 K, respectively, indicating no change in the tautomeric equilibrium.

In addition to the known NMR methods mentioned in a recent review,[10] dealing with the use of NMR spectroscopy to study tautomerism, the application of $^{n}J(^{15}N,^{15}N)$ coupling constants represents a new experimental tool that can be used in determining tautomeric structures, especially in symmetrical molecules similar to dihydro-1,2,4,5-tetrazines.

Acknowledgements

The authors thank VCI Brasil and the Ministry of Education, Youth and Sports of the Czech Republic (Grant No: MSM 0021627501) for the financial support.

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