Research Article

NMR $^1$H Spectra of the [1,2]Diazepino[4,5-b]Indole Derivatives: Experimental versus GIAO calculated Data

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Abstract

A comprehensive study of new [1,2]diazepino[4,5-b]indole derivatives molecular geometry as well as their NMR $^1$H spectra by DFT method was performed. GIAO-calculated NMR $^1$H chemical shifts as obtained at B3LYP/6-31G (d,p)/PCM computational level are reported for the 1,2-diazepine compounds.

Keywords: [1,2]Diazepino[4,5-b]indoles; B3LYP; GIAO; NMR $^1$H spectra; Chemical shift.

Introduction

The biological activity of compounds containing in their structure the 1-aryl-2,3-benzodiazepine skeleton is best demonstrated by the example of tofisopam, a well-known anxiolytic drug, or talampanel [1,2]. Related condensed heterocyclic systems, such as indolo-1,2-diazepines, can be considered as potentially useful structures for drug design. It is known that indole-condensed azacycles are structural components of many natural and synthetic biologically active compounds [3,4]. Investigations on the synthesis of indolo[1,2]diazepines are few [5-8] and limited to derivatives containing alkyl substituent’s in the diazepine ring. Synthesis and structural modification of aryl-containing indolodiazepines have been demonstrated recently [9]. As a continuation of our research on the synthesis and reactivity of heterocyclic systems based on 1,2-diazepine [8,10-12], this paper presents the results of molecular modeling of the structure and NMR $^1$H spectra of some new indolo[1,2]diazepines.

Experimental Part

NMR $^1$H spectra were recorded in DMSO-d$_6$ on 400/100 MHz NMR spectrometer (Bruker Avance II 400) and chemical shifts values ($\delta$) are given in parts per million relative to tetramethylsilane (TMS). The melting points were determined on a Boetius hot stage. The CHN elemental analysis was performed using a Varian MICRO Cube analyzer. The mass spectra were recorded on an Agilent 1100 LC/MSD VL instrument (atmospheric pressure chemical ionization; Zorbax SBC18 column, 50 x 4.6 mm; eluent acetonitrile-water (95:5) containing 0.1% of trifluoroacetic acid, flow rate 3.0 mL/min, gradient elution).

For detailed information on the synthesis of [1,2]diazepino[4,5-b]indoles 1-3 as well as their precursors, see our recent article [9].

1-(4-methylphenyl)-5,10-dihydro[1,2]diazepino[4,5-b]indol-4(3$H$)-one (1).

Yield 45%, M.p. 281-282°C. NMR $^1$H (DMSO-d$_6$), $\delta$, ppm: 2.42 s (3$H$, 4'-$\text{СН}_3$), 3.59 s (2$H$, $\text{СН}_2$), 7.06 t (1$H$, H-7, $J$ 8.0 Hz), 7.18 t (1$H$, H-8, $J$ 8.0 Hz), 7.24 d (2$H$, H-3',5'), 7.80 t (1H, H-7, J 8.0 Hz), 7.18 t (1H, H-8, J 8.0 Hz), 7.24 d (2H, H-3',5'), 7.80 t (1H, H-7, J 8.0 Hz),...
1-(4-methylphenyl)-5,10-dihydro[1,2]diazepino[4,5-b]indole-4(3H)-thione (2).

Yield 82%, M.p. 200-202°C. NMR 1H (DMSO-d6), δ ppm: 2.44 s (3H, 4'-CH3), 2.98 br. s (1H, CH2), 3.38 br. s (4H, NCH2CH2N), 3.61 br. s (4H, OCH2NCH2), 4.30 s (1H, CH), 7.04 t (1H, H-7, 8.0 Hz), 7.17 t (1H, H-8, 8.0 Hz), 7.24 d (2H, H-3',5', 8.0 Hz), 7.39 d (1H, H-9, 8.0 Hz), 7.70 d (3H, H-6, H-2',6', 8.0 Hz), 11.16 s (1H, NH). Mass-spectrum: m/z 359 [M+1]+. Found, %: C 77.10; H 5.25; N 14.52. Anal. Calcd. for C18H15N3O, %: C 74.72; H 5.23; N 14.52. The calculated magnetic isotropic shielding tensors, χ, were transformed to chemical shifts relative to TMS, δ, by δ=χref/χ, where both, χref and χ, were taken from calculations at the same computational level. χ Values for magnetically equivalent nuclei were averaged.

Results and Discussion

The main method of a 1,2-diazepine ring condensed with a heterocyclic fragment formation is the condensation of 1,5-dicarboxyl compounds with hydrazine [8,10-12]. Our approach to obtaining [1,2]diazepino[4,5-b]indoles 1-3 involves the synthesis of the starting 1,2-diazepine 1 and its subsequent structural modification to obtain compounds 2-3 (Figure 1).

The peculiarity of the NMR 1H spectrum of N-substituted 1,2-diazepin-4-thion 2 is the appearing of the methylene group protons as two broadened singlets with chemical shifts of 3.00 and 3.51 ppm (compound 3a) as well as 2.98 and 4.30 ppm (compound 3b). The structure of the obtained new compounds 1-3 was confirmed by NMR spectroscopy. The peculiarities of the NMR 1H spectrum of N-substituted [1,2]diazepino[4,5-b]indol-4-one 1 was obtained by cyclization of ethyl [2-(4-methylbenzoyl)-1H-indole-3-yl] acetic acid with hydrazine in the presence of a catalytic amount acetic acid. Then [1,2]diazepino[4,5-b]indol-4-one 1 was transformed to the corresponding thion 2 by reaction with Lawesson’s reagent. Diazepin-4-thion 2 interacts with corresponded amine when heated in propanol-2 with the formation of compounds 3a,b. The structure of the obtained new compounds 1-3 was confirmed by NMR spectroscopy.
1,2-diazepines 1-3 with the numbering of atoms used in the discussion of the calculated chemical shifts, are shown on figure 2.

Table 1. Parameters of calculated chemical shifts, are shown on figure 2. The calculated chemical shifts of the [1,2-diazepino[4,5-b]indoles 1-3 obtained by B3LYP/6-31G(d,p) method with PCM approximation (solvent - DMSO).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Diazepine 1</th>
<th>Diazepine 2</th>
<th>Diazepine 3a</th>
<th>Diazepine 3b</th>
</tr>
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<tbody>
<tr>
<td>C6-C8, Å</td>
<td>1.383</td>
<td>1.385</td>
<td>1.385</td>
<td>1.385</td>
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<tr>
<td>C6-C9, Å</td>
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<td>1.497</td>
<td>1.496</td>
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<tr>
<td>C8-C10, Å</td>
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<td>1.450</td>
<td>1.454</td>
<td>1.451</td>
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<tr>
<td>C9-C11, Å</td>
<td>1.519</td>
<td>1.513</td>
<td>1.521</td>
<td>1.523</td>
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<tr>
<td>C10-N2, Å</td>
<td>1.303</td>
<td>1.307</td>
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<tr>
<td>N2-N3, Å</td>
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<td>1.348</td>
<td>1.311</td>
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<td>N3-H8, Å</td>
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<td>1.382</td>
<td>1.364</td>
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<tr>
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<td>1.014</td>
<td>-</td>
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<tr>
<td>C11-H6, Å</td>
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<td>1.088</td>
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<tr>
<td>C11-H7, Å</td>
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<tr>
<td>δH1</td>
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<td>4.364</td>
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<td>2.96</td>
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<td>7.64</td>
<td>7.876</td>
<td>7.787</td>
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<td>δH10</td>
<td>11.12</td>
<td>7.493</td>
<td>7.430</td>
<td>7.443</td>
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<tr>
<td>Δδ exp, ppm</td>
<td>0.952 ± 0.09</td>
<td>0.953 ± 0.07</td>
<td>0.945 ± 0.15</td>
<td>0.945 ± 0.03</td>
</tr>
</tbody>
</table>

For the most stable conformers of the studied 1,2-diazepines molecules, the NMR 1H chemical shifts were estimated. To calculate the magnetic shielding constants using the standard GIAO method, the equilibrium configurations of compounds 1-3, obtained by B3LYP/6-31G(d,p) method with PCM approximation were used. The obtained chemical shifts for the compounds 1-3 are given in table 2. The NMR 1H parameters of the studied 1,2-diazepines are correctly reproduced at this theoretical level except for NH protons. It should be noted that taking into account non-specific solvation within PCM model is not sufficient for the correct reproduction of these protons, and the formation of hydrogen bonds with the solvent molecules should be considered. Thus chemical shifts of NH protons were not considered in further discussion. Linear relationships between the experimental chemical shifts and the calculated ones have been obtained for all studied diazepines molecules (Figure 3). The correlation coefficients (R) corresponding to obtained dependences are within 0.993–0.999. Equations, obtained for the individual compounds and the total one:

1. δexp=(0.952 ± 0.09)δcalc+(0.14 ± 0.06), R=0.99946;
2. δexp=(0.953 ± 0.07)δcalc+(0.15 ± 0.05), R=0.99966;
3a. δexp=(0.952 ± 0.037)δcalc+(0.09 ± 0.22), R=0.999317;
3b. δexp=(0.945 ± 0.015)δcalc+(0.18 ± 0.05), R=0.99735;
Total: δexp=(0.945 ± 0.013)δcalc+(0.18 ± 0.08), R=0.99628.

Table 2. Experimental (in DMSO-d6 solution) and calculated (B3LYP/6-31G(d,p)/PCM) NMR 1H chemical shifts of the [1,2-diazepino[4,5-b]indoles 1-3.

<table>
<thead>
<tr>
<th>Atom</th>
<th>Δδ exp, ppm</th>
<th>Δδ calc, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>0.952 ± 0.09</td>
<td>0.14± 0.06</td>
</tr>
<tr>
<td>H2</td>
<td>0.953 ± 0.07</td>
<td>0.15± 0.05</td>
</tr>
<tr>
<td>H3</td>
<td>0.945 ± 0.15</td>
<td>0.18± 0.05</td>
</tr>
</tbody>
</table>

Figure 2. Structural models of the [1,2]-diazepino[4,5-b]indoles 1-3 (B3LYP/6-31G(d,p)/PCM level) with atom labels used for calculated NMR 1H chemical shifts presenting for studied compounds.

Figure 3. Total linear correlation between the theoretical (GIAO, B3LYP/6-31G(d,p)/PCM level) and experimental (DMSO-d6 solution) proton chemical shifts of [1,2]-diazepino[4,5-b]indoles 1-3. (Chemical shifts of NH protons were not considered).
For N-substituted [1,2]diazepino[4,5-b]indoles 3a and 3b difference between calculated chemical shifts for non-equivalent methylene group protons exceeds the experimental value. This is due to the fast dynamics of the diazepine ring in the NMR time scale. With an increase in the temperature of the NMR experiment, one can expect higher conformation exchange rates, and, as a consequence, an even greater closing-in of these protons signals up to their coalescence. We observed such pattern for the 1,4-biaryl derivatives of benzofuro[2,3-d][1,2]-diazepines experimental NMR 1H spectra [17]. Thus, a comprehensive study of the 1,2-diazepine core dynamics of condensed diazepines by dynamic NMR spectroscopy as well as DFT method will be the next stage of our work.

Conclusion

A comprehensive study of the [1,2]diazepino[4,5-b]indole derivatives by experimental NMR 1H spectroscopy and molecular modeling methods was performed. Structural parameters of the studied diazepines compounds were obtained by B3LYP method. GIAO-calculated NMR 1H chemical shifts as obtained at B3LYP/6-31G(d,p)/PCM computational level are reported for the [1,2]diazepino[4,5-b]indoles. For NMR 1H spectra of the diazepines in DMSO-d6 this method approximation allows to obtain the correct spectral pattern. Linear correlations between the calculated and experimental values of the 1H chemical shifts for the studied molecules were obtained.

References