Letter - spectral assignment

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Complete ^{1}H NMR assignment of 3-formylindole derivatives

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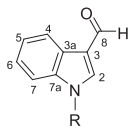
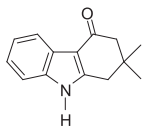
Introduction

3-Formylindoles including indolylglyoxylate esters and indolylglyoxylamides are widely found in nature as alkaloids,[1] and are important building blocks or synthetic intermediates for drug discovery,[2] and for the synthesis of natural products.[3] A careful inspection of the ^{1}H NMR data of these molecules[4] reveals that multiplicities for H4 and H7 are reported as broad doublets,[4a,4b] as doublet of doublets-*like*,[4b] as a combination of doublet of doublets and multiplets,[4a,4b] or simply as doublets.[4c,4d] In the case of H5 and H6, they are reported as triplet of doublets,[4a,4b] as triplets,[4c] or as doublet of triplets[4d] despite the fact that in most cases, their chemical shifts are claimed to be unambiguously assigned. In addition, incorrect coupling constant values for the incorrect multiplicities for H4–H7 are also reported. A prudent signal description of the H4–H7 system is rarely given as multiples without reporting coupling constant values.[4e]

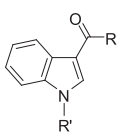
Consequently, we describe herein complete and accurate chemical shift and coupling constant assignments for H4–H7 in representative series, using compounds **1–10**, which followed after spectral analysis using the PERCH software and selective proton irradiations.



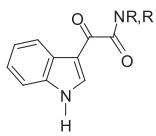
1: R = H
2: R = Me



3



4: R = OMe, R' = H
5: R = CO_2Me, R' = H
6: R = CO_2Bu, R' = H
7: R = R' = CO_2Me



8: R = Me, Me
9: R = *i*-Bu, H
10: R = *t*-Bu, H

Experimental

Compounds

Indoles **1** and **4**, commercially available molecules (Aldrich), were used without further purification, while indoles **2**, **5**, and **8–10** were obtained as described.[4a,5]

Preparation of 2,2-dimethyl-2,3-dihydro-1*H*-carbazol-4(9H)-one (3)[5b]

To a solution of dimedone (500 mg, 3.57 mmol) in trifluoroacetic acid (2.5 ml) was added phenylhydrazine (0.3 ml, 3.0 mmol), and the mixture was heated in a 10 ml sealed vessel at 144 °C for 10 min with microwave radiation in a monomode microwave reactor (CEM Discover BenchMate, United States of America) equipped with a built-in IR sensor and working at 300 W. After cooling to room temperature, the mixture was diluted with EtOAc (50 ml), washed with saturated aqueous $NaHCO_3$ solution (4 × 20 ml), brine (2 × 20 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resultant crude product was purified by flash chromatography on silica gel using EtOAc/hexanes (7:3 v/v) to afford **3** as a white solid (615 mg, 96%). Mp 209–210 °C (lit.[5c] 209–211 °C). ^{1}H NMR (see Table 1). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.0 (C8), 150.7 (C2), 136.1 (C7a), 124.7 (C3a), 123.2 (C6), 122.5 (C5), 121.2 (C4), 112.0 (C3), 111.2 (C7), 52.3 (C9), 37.3 (C11), 35.8 (C10), and 28.6 (Me).

Preparation of butyl 2-(1*H*-indoly-3-yl)-oxoacetate (6)[5e]

To a solution of **5** (30 mg, 0.14 mmol) in 5 ml of butanol was added LiBr (14 mg, 0.16 mmol) and *t*-$BuNH_2$ (170 mg, 2.3 mmol), and the mixture was stirred under reflux for 30 min. After cooling to room temperature, the volatiles were evaporated, and the residue was diluted with EtOAc (50 ml), washed with a saturated aqueous NH_4Cl solution (2 × 15 ml), dried over anhydrous Na_2SO_4, filtered, and evaporated to give **6** (38 mg, 99%). ^{1}H NMR (see Table 1). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.1 (C8), 165.0 (C9), 139.4 (C2), 137.8 (C7a), 126.6 (C3a), 125.0 (C6), 123.9 (C5), 122.2 (C4), 113.8 (C7), 113.4 (C3), 66.0 (C10), 30.6 (C11), 19.2 (C12), and 14.0 (C13).

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Table 1. Chemical shifts (300 MHz, TMS) and coupling constants (Hz) of indole derivatives **1–10**

	Compound									
	1[a]	**2**[b]	**3**[c]	**4**[d]	**5**[e]	**6**[f]	**7**[g]	**8**[h]	**9**[i]	**10**[j]
H-1	8.692	—	8.343	8.542	8.787	8.844	—	8.988	8.836	8.747
H-2	7.845	7.656	—	7.921	8.500	8.461	8.846	7.942	9.114	9.098
H-4	8.329	8.302	8.213	8.194	8.454	8.450	8.402	8.357	8.431	8.419
H-5	7.325	7.323	7.256	7.279	7.356	7.349	7.418	7.328	7.344	7.337
H-6	7.335	7.352	7.233	7.274	7.342	7.335	7.446	7.314	7.320	7.314
H-7	7.440	7.355	7.337	7.414	7.448	7.447	8.215	7.419	7.439	7.432
$J_{1,2}$	3.10	—	—	2.99	3.25	3.27	—	3.21	3.26	3.24
$J_{1,4}$	0.70	—	0.69	0.74	0.69	0.71	—	0.67	0.69	0.69
$J_{2,6}$	0.35	—	—	0.36	—	—	0.32	—	0.32	0.28
$J_{4,5}$	8.01	8.00	7.93	8.08	8.06	8.04	7.99	8.01	8.03	8.04
$J_{4,6}$	1.19	1.16	1.19	1.20	1.22	1.18	1.29	1.19	1.20	1.18
$J_{4,7}$	0.82	0.85	0.79	0.80	0.80	0.79	0.77	0.80	0.79	0.79
$J_{5,6}$	7.20	7.17	7.22	7.15	7.213	7.21	7.30	7.20	7.20	7.21
$J_{5,7}$	0.95	0.94	0.96	0.97	0.99	0.99	1.02	0.98	1.00	1.00
$J_{6,7}$	8.25	8.31	8.24	8.25	8.18	8.20	8.43	8.23	8.18	8.18
RMS (%)	0.092	0.100	0.095	0.098	0.108	0.098	0.063	0.073	0.095	0.107

[a]CHO 10.082, $J_{4,CHO}$ 0.26, $J_{5,CHO}$ 0.16.
[b]CHO 9.989, Me 3.860, $J_{4,CHO}$ 0.24, $J_{2,Me}$ 0.30.
[c]$COCH_2$ 2.471, CH_2 2.837; 2Me 1.551 and 1.178.
[d]CO_2Me 3.926.
[e]CO_2Me 3.959.
[f]$OCH_2CH_2CH_2Me$ 4.359, 1.784, 1.472, 0.973.
[g]CO_2Me 3.986, NCO_2Me 4.126.
[h]2Me 3.103 and 3.071.
[i]NH 10.175, $CH(Me)CH_2Me$ 3.971, (1.237), 1.588, 0.962.
[j]NH 5.996, 3Me 1.463.

Preparation of methyl 3-(2-methoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate (7)[5f]

A solution of indole **5** (200 mg, 0.98 mmol) in dry DMF (5 ml) was stirred under nitrogen at 0 °C, and NaH (35 mg, 1.46 mmol) was added portionwise. After 30 min, methyl chloroformate (46 mg, 0.5 mmol) was added, and the reaction mixture was stirred under reflux for 28 h. After cooling to room temperature, the volatiles were evaporated, and the residue was diluted with EtOAc (50 ml), washed with a saturated aqueous NH_4Cl solution (3 × 20 ml) and brine (3 × 20 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resultant crude product was purified by flash chromatography on silica gel using EtOAc/hexanes (1:4 v/v) to afford **7** as white solid (111 mg, 43%). Mp 118–119 °C. ^{1}H NMR (see Table 1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5 (C=O), 162.1 (CO_2Me), 150.5 (NC=O), 136.7 (C2), 135.2 (C7a), 127.2 (C3a), 126.3 (C6), 125.2 (C5), 122.5 (C4), 116.8 (C3), 114.9 (C7); IR (KBr), ν_{max} 3173, 2955, 1756, 1730, and 1662 cm^{-1}. EIMS *m/z* (relative intensity) 261 ([M]$^+$, 31), 202 (100), 158 (17), 143 (7); Anal. Calcd for $C_{13}H_{11}NO_5$: C 59.77, H 4.21, N 5.36. Found: C 60.02, H 4.19, N 5.10.

NMR Measurements

^{1}H NMR spectra were obtained on a Varian Mercury 300 (United Satates of America) instrument with a spectrometer frequency (SF) = 300.07 MHz at 303.1 K. Samples of 3–5 mg were dissolved in 0.9 ml of $CDCl_3$ and degassed by slow bubbling of Ar under ultrasound during 15 min. A final volume of 0.5 ml of $CDCl_3$ was left to which a small amount of TMS in $CDCl_3$ was added. The pulse conditions for the ^{1}H NMR spectra were as follows: acquisition time (AQ) = 10 s, relaxation delay (RD) = 1 s, 45° pulse width = 8.8 μs, spectral width (SW) = 4800.8 Hz. FT size = 128 k data. Manual shimming was performed until the TMS signal showed a linewidth at half height better than or equal to 0.19 Hz. The NMR data were processed on a Dell Precision T34300 workstation using the VNMR 6.1c software. Spectra were processed using only a baseline correction. Routine ^{13}C NMR spectra for the characterization of **3**, **6**, and **7** were determined at 100 MHz on a Varian VNMRS 400 spectrometer.

X-ray diffraction analysis of 7

Data were acquired on a Bruker Smart 6000 CCD diffractometer using Mo *Kα* radiation (λ = 0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. These data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. An empirical absorption correction was applied. Crystal data were $C_{13}H_{11}O_5N$, M = 261.23, monoclinic, space group $P2_1/n$, a = 7.5592(6) Å, b = 16.409(1) Å, c = 10.3460(8) Å, β = 109.14(3) V = 1212.3(4) Å^3, Z = 4, ρ = 1.43 mg/mm^3, μ(Mo *Kα*) = 0.112 mm^{-1}, total reflections = 8178, unique reflections 2387 (R_{int} 0.01%), observed reflections 1433, final R indices [$I > 2\sigma(I)$] R1 = 4.7%, and wR2 = 11.8%. The structure was solved by direct methods using the SHELXS-97[6] program, included in the WINGX v1.6[7] package, and refined by full-matrix least squares on F^2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms included in the structure factor calculation were refined isotropically. Crystallographic data

(excluding structure factors) have been deposited under number 1014480 at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Results and discussion

In order to obtain accurate chemical shift and coupling constant values for H4–H7 of 3-formylindole derivatives, unsubstituted at the benzenoid ring, iterative quantum mechanical spectral analysis, using the PERCH software, was selected. This procedure has allowed knowing small long-range coupling constant values in series of indoles, coumarins, and flavones substituted with one methoxy group,[8a] and in tropanes.[8b] The ^{1}H NMR chemical shifts and coupling constants for **1–10** are shown in Table 1. As already detailed,[8,9] PERCH calculations provide chemical shifts with six significant figures after the decimal point and coupling constants with four significant figures after the decimal point. In the present case, experimental spectra follow from measurements with magnetic

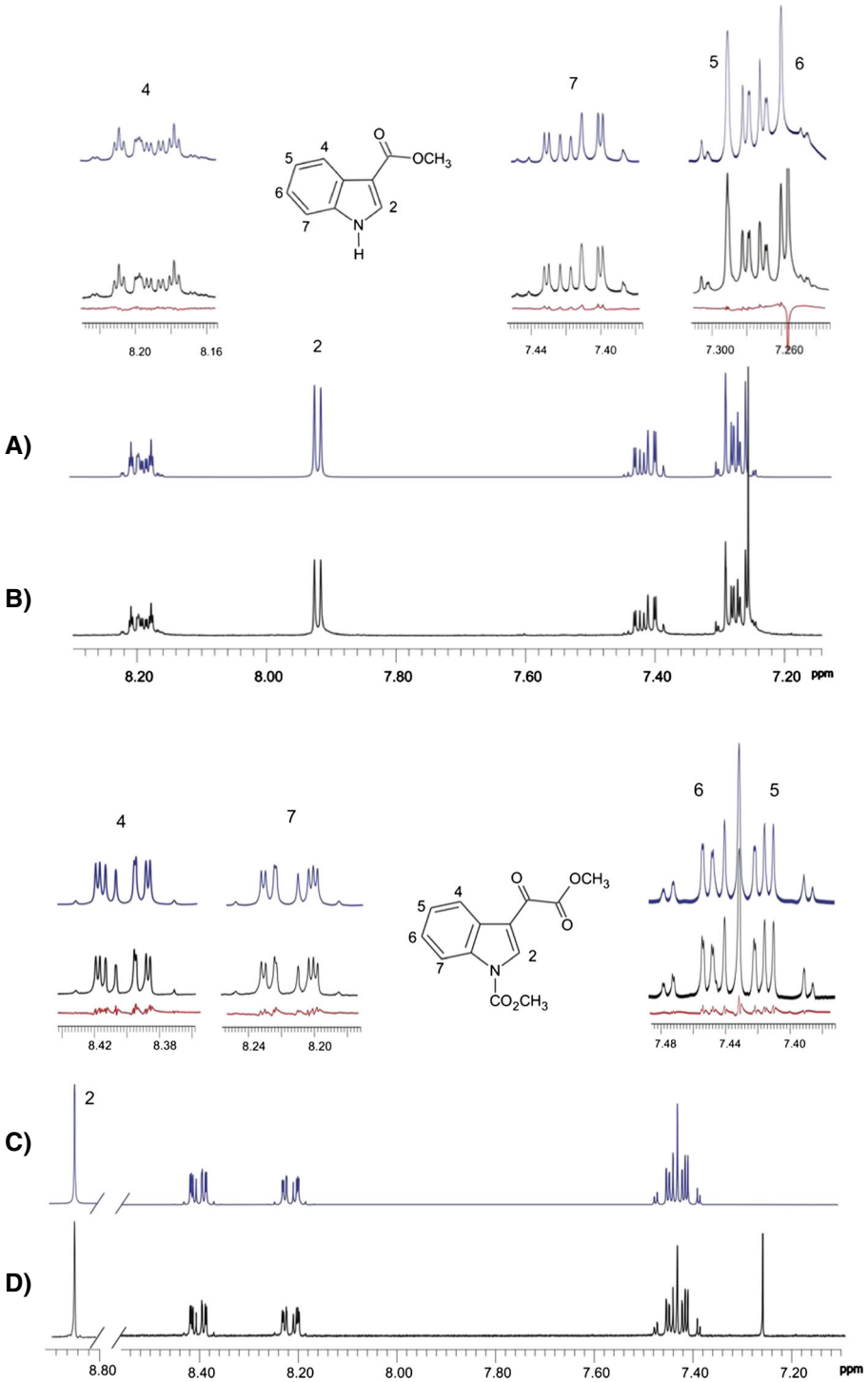


Figure 1. Experimental ^{1}H NMR spectra of **4** (B) and **7** (D) in $CDCl_3$ and simulated spectra of **4** (A) and **7** (C) using the PERCH software.

homogeneity equal or better than 0.19 Hz, and therefore, chemical shifts with three figures and coupling constants with two, both after the decimal point, are justified,[8,9] as given in Table 1. This also allows knowing the magnitudes of long-range coupling constants.

Figure 1 shows the representative experimental spectra for indoles **4** and **7**, as well as their corresponding simulated spectra using the PERCH software. The chemical shifts of H4 and H7 in compounds **1–6** and **8–10** can easily be differentiated because of the anisotropic effect of the C8=O carbonyl group on H4, giving rise to chemical shift at higher frequencies (8.194–8.454 ppm) than those of H7, which occur at 7.337–7.448 ppm (Fig. 1, top for **4**). This assignment is consistent with the H4 and H7 chemical shifts for indole **7** in which the signal for H7 appears at 8.215 ppm (Fig. 1, bottom) as a consequence of the anisotropic effect of the carbonyl group substituent at the N1 position.[10] Another useful option to differentiate between the H4 and H7 signals would be, provided adequate solubility, the correlation with their respective carbon atoms in $^{1}J_{C-H}$ correlated spectra because in indole derivatives, C7 has a significant upfield shift relative to all other protonated benzenoid carbon atoms.[11] In the case of **7,** it is important to note that the crystal structure (Fig. 2) reveals the proximity of the carbonyl groups to both H4 and H7.

Further, to differentiate H4 and H7, for *N*-unsubstituted indoles **1**, **3–6,** and **8–10**, we found in this work, in addition to the H1–H2 coupling, a selective H1–H4 long-range coupling (Table 1), which is also a useful tool to differentiate H4 from H7, as is shown in Fig. 3 for **1**, because saturation of H1 only affects the multiplicity of H4. Careful inspection of the traces reveals that upon irradiation of the NH frequency (top trace), the H5–H7 signals in the 7.5–7.3 ppm region do not change, while the H4 signal in the 8.4–8.3 ppm region shows clear sharpening of peaks. Finally, in the case of *N*-methyl-3-formylindole (**2**), irradiation of the methyl group in an 1D-NOESY experiment causes improvements to the signals at 7.355 (H7) and 7.656 ppm (H2).

The H2 chemical shifts of secondary glyoxylamides **9** and **10**, at 9.114 and 9.098 ppm, respectively (Table 1), are in agreement with monosubstituted *N*-alkylglyoxalylamides, which adopt the *syn* conformation in which the *N*-alkyl group is orientated *cis* to the amide

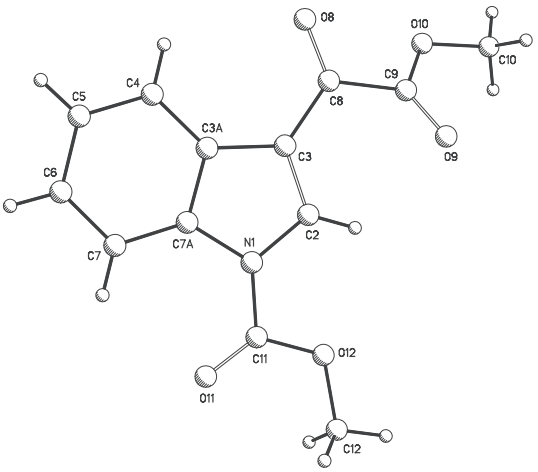
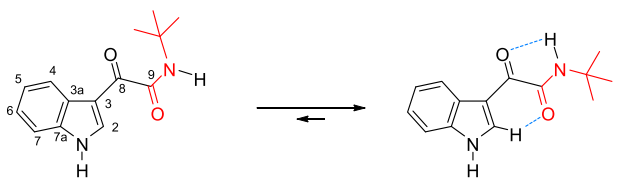


Figure 2. X-ray diffraction structure of **7**.



Scheme 1. Preferred conformation of indolylglyoxylamide **10**.

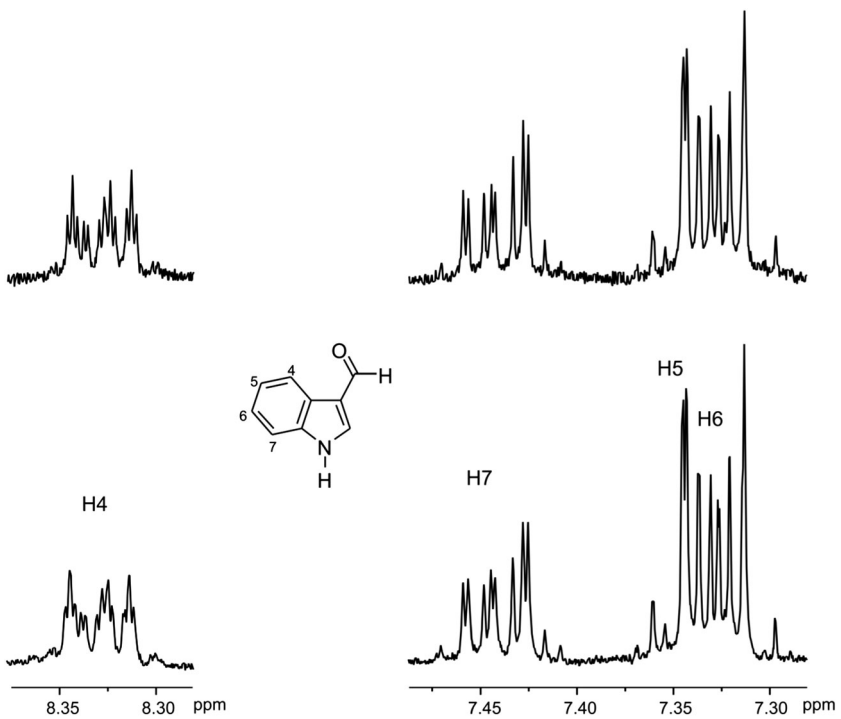
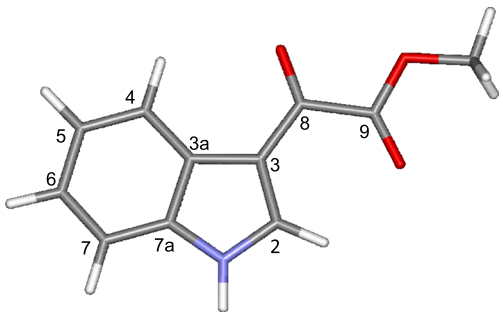


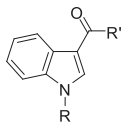
Figure 3. ^{1}H NMR spectra of the benzenoid portion of **1** showing the $^{5}J_{H1H4}$ coupling by irradiation of the NH signal (top).



E = -442407.43 kcal mol^{-1}
p = 99.8%

Figure 4. Optimized geometry, calculated energy (E/kcal/mol), and population (p in %) for **5** obtained at the DFT B3LYP/6-31G(d) level of theory.

Table 2. Chemical shift differences δ_5–δ_6 (Hz) and coupling constants $^{3}J_{5,6}$ (Hz) for indole derivatives **1–10**



			Hz at 300 MHz			Hz at 750 MHz
	R	R′	δ_5–δ_6	$^{3}J_{5,6}$	$\Delta\delta/J$	$\Delta\delta/J$
1	H	H	−2.92	7.20	−0.41	−1.01
2	Me	H	−8.64	7.17	−1.21	−3.01
3	H	ketone	6.90	7.22	0.96	2.39
4	H	OMe	1.33	7.15	0.19	0.46
5	H	CO_2Me	4.26	7.21	0.59	1.47
6	H	CO_2Bu	4.15	7.21	0.57	1.44
7	CO_2Me	CO_2Me	−8.33	7.30	−1.14	−2.85
8	H	CONMe,Me	4.38	7.20	0.61	1.52
9	H	CONH,*i*-Bu	7.19	7.20	1.00	2.50
10	H	CONH,*t*-Bu	6.86	7.21	0.95	2.38

carbonyl group (Scheme 1).[4a] This preferred conformation is attributed to the presence of two sets of intramolecularly hydrogen-bonded rings as is shown for **10** in Scheme 1, in which the hydrogen-bonded five-membered ring from the amide NH to the keto group controls the O=C8–C9=O torsion angle, which is closer to the *trans*-coplanarity, facilitating a close approach of the C9=O carbonyl to H2, giving rise to a deshielding of the latter. We also found that the intramolecular hydrogen bonds for **9** and **10** could be further evidenced when comparing the H2 chemical shift of both compounds in $CDCl_3$ solutions,[12] at 9.114 and 9.098 ppm (Table 1), with those reported in DMSO-d_6 solutions, at 8.69 and 8.72 ppm, respectively,[12a] because secondary glyoxylamides do not associate in solution.[12b] On the contrary, tertiary glyoxylamide **8** lacks the ability to form the intramolecular hydrogen-bonded five-membered ring, because the O=C8–C9=O fragment is out of planarity, and therefore, the signal for H2 appears at lower frequencies[13] (7.942 ppm).

In 3-formylindole derivatives **1**, **2,** and **4**, H2 appears at low frequencies (7.656–7.921) as in **8** (7.942 ppm). This evidences that H2 could not be highly influenced by the anisotropic effect of the C8=O carbonyl group, which is mainly oriented toward H4. A different situation occurs for indolylglyoxylates **5** and **6**, in which H2 appears at higher frequencies (8.500 and 8.461, respectively) than in glyoxalylamides **9** and **10**. To explain the chemical shift values of H2 for **5** and **6**, a systematic molecular modeling protocol, using a Monte Carlo searching[14] and geometry optimization by density functional theory calculations at the B3LYP/6-31G(d)[15] level of theory, was applied to **5**. Initial Monte Carlo search at the MMFF94[16] molecular mechanics force field level, as implemented in the Spartan08 (CA, USA)[17] program, afforded four conformers for **5** in the first 0.60 kcal/mol energy gap. The four structures were submitted to geometry optimization using density functional theory calculations at the B3LYP/6-31G(d) level of theory giving almost exclusively (99.8%) the conformer shown in Fig. 4, in which the O=C8–C9=O torsion angle is *trans*-coplanar with a C3–C8–C9=O dihedral angle of 0.48°, causing the C9=O carbonyl to be oriented toward H2. Thus, indoles **5–7**, **9,** and **10** should present the same preferred conformation at the O=C8–C9=O fragment as suggested in Fig. 2 where indole **7** shows the *trans*-coplanarity (−37.1°) preference for this fragment in the solid state. By taking into consideration all of these observations, it follows that the

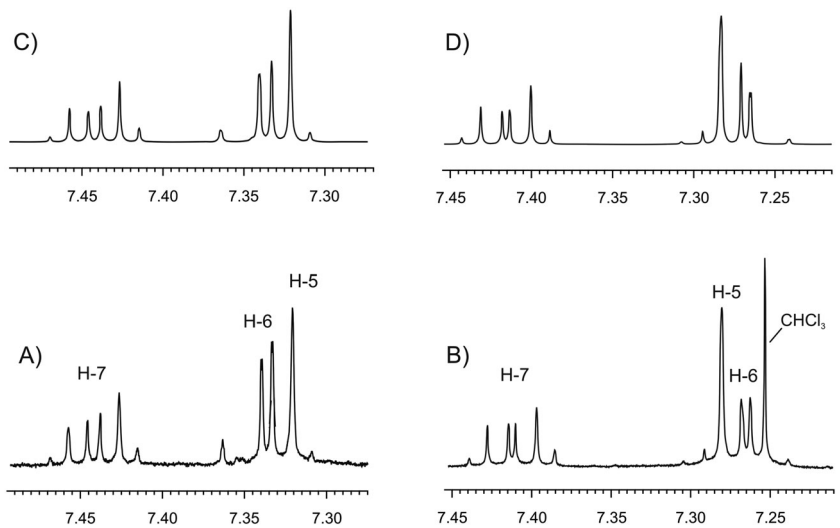


Figure 5. Lower traces: experimental sub-spectra of **1** (A) and **4** (B) on irradiation of H4. Upper traces: spin analysis by PERCH iteration at 300 MHz of **1** (C) and **4** (D).

highly coupled H4–H7 spin–spin system is influenced by the planarity of the R–N1–C2=C3–C8=O fragment.

Regarding H5 and H6, Table 2 shows the $^3J_{5,6}$ and δ_5–δ_6 values in Hz. As can be seen, the $\Delta\delta/J$ relationships at 300 MHz evidence strongly coupled spectra for compounds **1–10**, and that this situation will not change at higher magnetic fields, as evident for the estimated $\Delta\delta/J$ values at 750 MHz, the highest frequency to which we have access. Table 1 also shows that for some compounds, H5 appears at lower chemical shifts than H6, but for other compounds, the reverse situation holds. Thus, special care should be taken when assigning the chemical shifts of these protons. A simple way to know the H5 and H6 chemical shift order is by irradiation of H4. In the case of **1,** this results in an intense signal at the lower frequency portion of the H5–H6 multiplets (A and C in Fig. 5), while the reversed situation occurs in the case of **4** (B and D in Fig. 5).

In conclusion, it turned out that the aromatic signal multiplicity pattern for H4–H7 corresponds to a strongly coupled system because the magnitude of $^3J_{H5H6}$ is larger than the δ_{H5}–δ_{H6} value (in Hz), and therefore, the multiplicity pattern cannot be analyzed as for first order spectra.

Acknowledgements

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