

The Investigation of ^1H NMR Spectra of 2,3-Dihydro-4-Pyridinones Derived from Bisdemethoxycurcumin

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Abstract: Problem statement: The studied dihydropyridones were synthesized via microwave assisted reaction of bisdemethoxycurcumin and amines or amine acetates which is new approach in the synthesis of this important class of compounds and the deep study of their NMR spectra seems reasonable. **Approach:** ^1H NMR spectra of dihydropyridones derived from curcumin were discussed and their structures were elucidated accordingly. **Results:** The one dimensional, HOMO-and HETERO-COSY spectra indicated the presence of two doublets of doublets signals of two geminally coupled protons with ^2J values of 16 Hz. Both these protons coupled to the same vicinal proton within a six-membered ring with ^3J coupling constants of ^3J values of 7 and 4 Hz. Computational calculations using B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p) level of theory were undertaken to predict the chemical shifts of one molecule via the GIAO method. **Conclusion:** The above mentioned theoretical method affords good approach for the prediction of the NMR spectra of the studied compounds.

Key words: Bis-demethoxycurcumin, dihydropyridones, geminal coupling, DFT, GIAO method

INTRODUCTION

Dihydropyridones are important intermediates for the synthesis of natural products, particularly alkaloids and have been extensively investigated as valuable building block for the construction of piperidines, perhydroquinolines, indolizidines, quinolizidines and other alkaloid ring systems with a wide range of biological and pharmacological properties (Cabrera *et al.*, 2010; Sax *et al.*, 2005; 2006; Van Otterlo and de Koning, 2009). For their synthesis the addition of Grignard reagents to 1-acyl-4-methoxypyridinium salts has been generally exploited by Comins *et al.* (1990); Kuethe and Comins (2003); Young and Comins (2005) and McCall *et al.* (2008). Hetero-Diels-Alder reactions or stepwise, formal [4+2] transformations involving imines have been employed (Waldmann and Braun, 1992; Huang and Rawal, 2000; Alaimo *et al.*, 2008). Recently their synthesis from the cyclization of α,β -unsaturated 1,3-diketones in acidic medium was reported (McDonald and Burnell, 2009). They were also synthesized through catalytic metathesis of *o*-alkynylanilines and aldehydes (Saito *et al.*, 2009). A facile route to functionalized dihydropyridones have been developed via formal [5C+1N] annulations of α -alkinoyl ketene-(S,S)-acetals with aliphatic amines (Dong *et al.*, 2005). The partial reduction of pyridinium salts have been also exploited for their synthesis (Donohoe *et al.*, 2009). In this connection, we reported the microwave assisted formation of 2,3-dihydro-4-

pyridinones from curcumin and simple primary amines in the presence of Montmorillonite K-10 via transient imine (Elias *et al.*, 2008). On the other hand, bisdemethoxy-curcumin, is an α,β -unsaturated 1,3-diketone that constitutes one of the three major components of the Indian herb *Curcuma longa* (Portes *et al.*, 2007; Scotter, 2009). The aim of this work is to investigate the NMR spectra of dihydropyridones derived from bis-demethoxycurcumin and amines under microwave irradiation.

MATERIALS AND METHODS

The synthesis of the studied compounds was previously described (article accepted for publication in Tet. Lett.). NMR spectra were recorded with a Bruker WM-400 (400 MHz) spectrometer in d_6 -DMSO with Tetramethylsilane (TMS) as an internal standard. For theoretical calculations the structure of molecule 1 was fully optimized with B3LYP functional at the 6-31G(d,p) basis set. The ^1H NMR spectra were predicted using B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p) level of theory using the GIAO method.

RESULTS

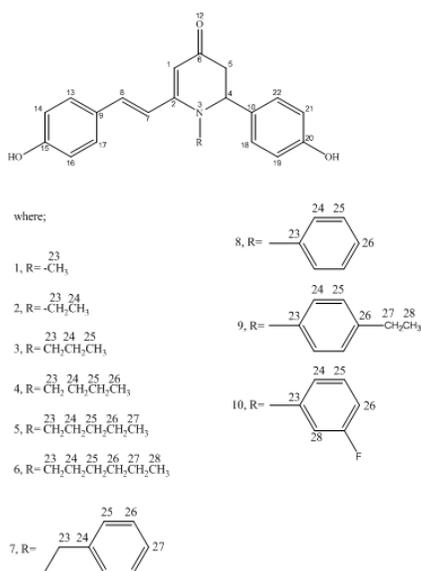
The molecular structures of the studied compounds are shown in Scheme 1. The spectral experimental data are gathered in Table 1 and some characteristic spectra are shown in Fig. 1 and 2. A plot for the calculated versus the experimental spectra is shown in Fig. 3.

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Table 1: Chemical shifts (δ , ppm) ^1H NMR of the studied compounds

Compd.	1	2	3	4	5	6	7	8	9	10
H5	2.34dd	2.35dd	2.26dd	2.32dd	2.26dd	2.34dd	2.38dd	2.66dd	2.51dd	2.34dd
	2.87dd	2.81dd	2.83dd	2.83dd	2.80dd	2.83dd	2.82dd	3.08dd	3.09dd	2.83dd
H4	4.65m	4.71m	4.70m	4.70m	4.66m	4.70m	4.68m	5.10m	5.06m	5.04m
H1	5.10s	5.06s	5.02s	5.04s	5.01s	5.04s	5.16s	5.10s	5.39s	5.04s
H19	6.74	6.71	6.67	6.71	6.71	6.70	6.19-7.25m	6.70-7.48m	6.19-7.21m	6.70-7.48m
H14	6.79d	6.78d	6.74d	6.76d	6.75d	6.74d	6.19-7.25	6.70-7.48m	6.19-7.21m	6.70-7.48m
H7	6.91d	6.91d	6.89d	6.88d	6.91d	6.89d	6.19-7.25m	6.70-7.48m	6.19-7.21m	6.70-7.48m
H18	7.07d	7.09d	7.04d	7.06d	7.06d	7.07d	6.19-7.25m	6.70-7.48m	6.19-7.21m	6.70-7.48m
H8	7.17d	7.17d	7.14d	7.15d	7.15d	71.5d	6.19-7.25m	6.70-7.48m	6.19-7.21m	6.70-7.48m
H13	7.53d	7.50d	7.48d	7.48d	7.49d	7.49d	6.19-7.25m	6.70-7.48m	6.19-7.21m	6.70-7.48m
H23	3.05s	3.08m	3.09 m	2.96 m	2.90m	2.96m	-	-	-	-
		3.75m	3.73 m	3.77m	3.74m	3.76m	-	-	-	-
H24	-	1.09t	1.52m	1.50m	1.49m	1.51m	-	-	-	-
H25	-	-	0.80t	1.25m	1.18m	1.20m	-	-	-	-
H26	-	-	-	0.83t	1.18	1.20m	-	-	-	-
H27	-	-	-	-	0.59t	1.20m	-	-	-	-
H28	-	-	-	-	-	0.77t	-	-	-	-
OH	9.41s	8.29s	8.29s	8.30s	8.30s	8.35s	8.46s	8.35s	8.38s	8.40s
	9.82s	9.48s	9.48s	9.51s	9.51s	9.57s	9.39s	9.57	9.55s	9.59s

s: singlet d: doublet dd: doublet of doublets t: triplet m: multiplet



Scheme 1: The molecular structures of the studied compounds

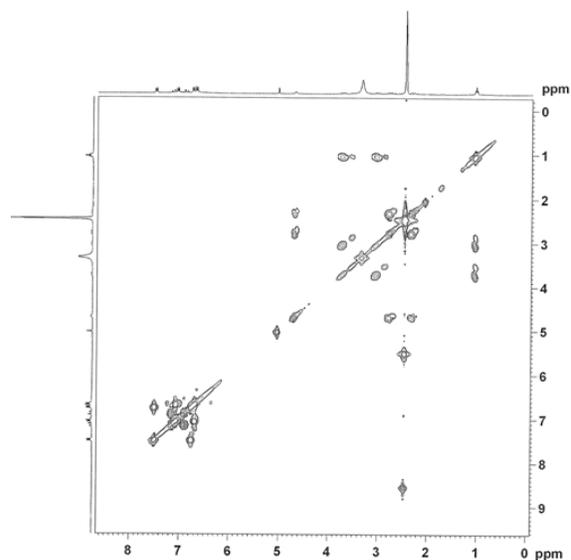


Fig. 2: The HOMO-COSY ^1H NMR spectrum of compound 2

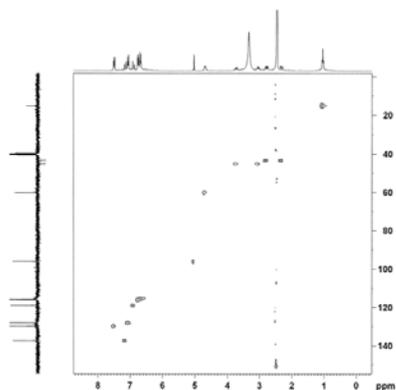


Fig. 1: The HETCOR spectrum of compound 2

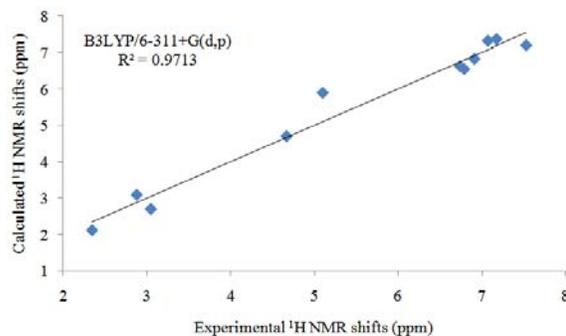


Fig. 3: Plot of the calculated Vs the experimental ^1H NMR chemical shifts (ppm) for compound 1

DISCUSSION

It is well known that the ^1H NMR spectrum of bis-demethoxycurcumin contains one singlet at 9.69 ppm due to the protons of two hydroxyl groups which reflects its symmetric structure. Concerning the studied compounds the spectra are characterized by two singlets with an integral of one proton for each signal at chemical shifts around that of the hydroxyl groups of bis-demethoxycurcumin. In compound 1 this signals appear at 8.29 and 9.48 ppm which are assigned to two hydroxyl groups at different environments. The spectra are also characterized by a singlet of one proton integral at the range 5.01-5.39 ppm (Table 1) which is assigned to the vinylic proton. The most important signals which give aid to elucidate the molecular structure of the compounds are those arise within the ranges 2.26-2.66, 2.80-3.09 and 4.65-5.10 ppm each of them has the integral of one proton. In the spectrum of compound 2 they are appear at 2.43, 2.84 and 4.66 respectively. The first two signals are both doublets of doublets with coupling constants 16 and 4 and 16 and 7 Hz respectively. The J-coupling values suggest that these are belonging to two coupled protons. In addition their positions at the saturated side of the spectrum and their coupling values (16 Hz) mean that they are geminal protons. Being further split with different coupling constants suggests that the protons are coupled to a common proton which attains different angles with them. According to the splitting fashion of the peak at 4.66 ppm it could be concluded that this peak is that of the proton of choice. The HETCOR spectrum of compound 2 is shown in Fig. 1. It is clear that the two protons of the peaks at 2.35 and 2.81 ppm are connected to the same carbon atom which has a peak at 42.0 which confirms that they are geminal protons. Meanwhile the proton of the peak at 5.03 ppm is connected to the olefin carbon with a peak at 96.2 ppm confirming its vinylic nature.

Figure 1 also shows that the two peaks at 3.08 and 3.75 ppm are connected to the carbon of the peak at 51.5 ppm which is assigned to the N-C carbon. This suggests that the N-CH₂-protons of the propyl chain are diastereotopic. The HOMO-COSY spectrum of compound 2 is shown in Fig. 2. It could be seen that both protons at C5 are coupled to each other at the same time they coupled to the proton at C4 since they have cross peaks. The diastereotopic property of the N-CH₂ protons is confirmed in Fig. 2, since there are cross peaks for their peaks at 3.08 and 3.75 ppm. According to the foregoing discussion and comparing the NMR spectra of the studied compounds with the spectrum of the corresponding dihydropyridone that synthesized by

Sugiyama *et al.* (1970) which has chemical shifts at 2.75, 3.31, 5.14, 5.20 and 6.42 ppm for the protons at C5, C1, C8 and C7 respectively, the suggested structures for the studied compounds seems understandable. The optimized structure of compound 1 was used to calculate ^1H chemical shifts at the level B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p) using the GIAO method. In order to compare the experimental and theoretical chemical shifts, the correlation graphic based on the calculations have been presented in Fig. 3. The correlation value of the proton chemical shifts is found to be 0.9854. The calculated chemical shift for the OH proton found to be 4.01 and 4.12 ppm which underestimated compare to the experimental values (9.41 and 9.82 respectively). This may rationalized on the basis that experimental chemical shifts of this proton depends on many things such as the solvent used, the temperature, the concentration and the hydrogen bonding in solution, while the theoretical calculations are done for the gas phase. Accordingly the OH proton signal not included in Fig. 3.

CONCLUSION

The study indicated that the main features of the spectra of the studied dihydropyridones are the signals of the two geminal protons attached to C5 which are appear as two doublets of doublets within the ranges 2.26-2.66 and 2.80-3.09 ppm with coupling constants of 16, 7 and 4 Hz. These protons are both coupled the proton at C4 which characterized by a multiplet signal and appears within the range 4.65-5.10 ppm. In addition the spectra are characterized by the signal of the vinylic proton which appears within the range 5.01-5.39 ppm.

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