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An Unusual Seven-Bond H–H Spin Coupling

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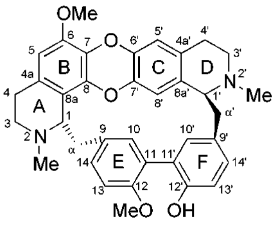
ABSTRACT



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A through-space, seven-bond ^1H–^1H coupling has been observed in tiliacorinine (1) caused by the close spacial proximity of two aromatic protons that are located in different benzene rings which are separated by two sp^3 carbons. Results from DQF-COSY and NOESY NMR experiments, as well as molecular modeling, reveal that the two protons are unusually close to one another in space.

In NMR spectroscopy, spin−spin interactions between the same or different nuclear species can reveal a variety of structural information. Spacial relationships between protons in a molecule can be typically deduced from measurement of nuclear Overhauser effects. In certain specific instances, through-space proton−proton spin−spin coupling has been used for this purpose.[1] In the present Letter, we wish to report the observation of an unusual seven-bond spin coupling (0.4 Hz) between the resonances of two aromatic protons located on two different benzene rings that are formally separated by two sp^3 carbon atoms. We initially discovered such a long-range coupling in 1976,[2] while examining the proton NMR spectra (100 MHz) of several alkaloids. These alkaloids were extracted from the same plant source: *Tiliacora racemosa* Colebr. (Menispermceae), a woody climber that grows in the subtropical regions of India where the plant is regarded as an antidote for snake bite. Additionally, it should be pointed out that all alkaloids under study possess the same gross structure, namely, a dibenzo-*p*-dioxin-containing bisbenzylisoquinoline with a diphenyl unit (Figure 1).[3]

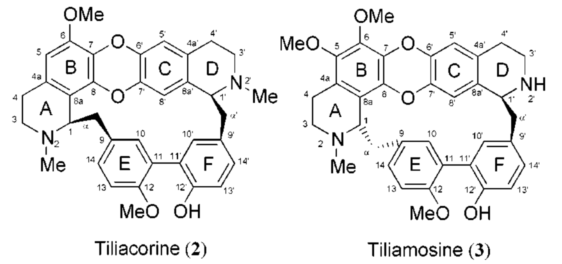

Figure 1. Tiliacorine and tiliamosine.

In the 1976 study, our objective was to determine the gross structure, as well as the stereochemical nature, of the newly

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(1) For example, see: Schroeder, H.; Haslinger, E. *Magn. Reson. Chem.* **1994**, *32*, 12−15.

(2) Quhs, K. P.; Das, P. C.; Mukkerjee, B.; Mukkerjee, R,; Juneau, G. P.; Bhacca, N. S. *Tetrahedron Lett.* **1976**, 4241−4244.

(3) For a comprehensive review of the bisbenzylisoquinoline alkaloids, see: (a) Barbosa-Filho, J. M.; Da-Cunha, E. V. L.; Gray, A. I. In *Alkaloids of the Menispermmaceae*; Cordell, G. A., Ed.; The Alkaloids: Chemistry and Biology, Volume 54; Academic Press: San Diego, CA, 2000; Vol. 1, pp 1−190. (b) Schiff, P. L. *J. Nat. Prod.* **1997**, *60*, 934−953.

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isolated alkaloid tiliamosine (**3**), $C_{36}H_{36}N_2O_6$, which possessed strong hypotensive properties. We had hoped to accomplish this task through a comparison of the proton NMR spectral data of **3** and its derivatives with those of the two diastereoisomers tiliacorinine (**1**) and tiliacorine (**2**), $C_{36}H_{36}N_2O_5$, alkaloids of known structures. Such a comparison revealed that **3**, the alkaloid possessing an extra oxygen atom, is actually a derivative of **1**. The methyl group situated on the nitrogen atom, present in the saturated ring D in **1**, moves to the aromatic ring B in **3**. Also, replacement of the aromatic hydrogen atom on ring B in **3** shifts to the nitrogen atom in ring D (Figure 1). However, more importantly, this study demonstrated that the proton NMR spectra of both **1** and **3** contain an unusual seven-bond, through-space coupling of 0.4 Hz between the resonances of H-8′ located on the ring C and H-10′ situated on the ring F. The two benzene rings C and F are separated by two sp^3 carbon atoms in both molecules (Figure 1).

The occurrence of such an unusual coupling was established by conducting double resonance experiments on the following proton resonances: (i) When the broad doublet at $\delta = 7.61$ representing H-10′ was irradiated, there was ~0.4 Hz decrease in linewidth of the singlet at $\delta = 8.10$ which corresponds to H-8′. (ii) Conversely, there was ~0.4 Hz decrease in the linewidth of the H-10′ resonance when the H-8′ signal was irradiated (Figure 2).

At the time of our earlier NMR investigation, we were unable to perform analogous double-resonance experiments to observe the spin−spin interactions between H-8′ and H-10′ in the second diasteromer **2**. The close proximity and the overlap of the relevant proton signals in the 100 MHz spectrum of **2** made the double-resonance experiments untenable. Hence, this interesting long-range coupling study remained half-completed, dormant, and almost forgotten. Recently, we resurrected the project by subjecting **2**, as well as **1**, to 2D NMR (DQF-COSY and NOESY) examination at 400 MHz. The results of these experiments were then compared with our earlier NMR data obtained at 100 MHz.

The DQF-COSY experiments conducted on the two diastereoisomers clearly showed (i) that there is no spin−spin interaction among the H-8′ and H-10′ resonances in **2** and (ii) provided confirmation of the presence of spin−spin coupling between the resonance of H-8′ and H-10′ in **1**. The double-resonance experiments performed at 400 MHz also confirmed the magnitude of the long-range coupling between the H-8′ and H-10′ resonances, as was determined earlier at 100 MHz.

Nuclear Overhauser enhancements (NOE) at 100 MHz and the 2-D NOESY at 400 MHz (Figure 2) experiments conducted on the two diastereoisomers revealed close spatial relationships of the following specific aromatic protons on rings C, E, and F: H-8′ on ring C with H-10′ on ring F, H-8′ on ring C with H-10 on ring E, and H-10′ on ring F with H-10 on ring E.

In **1** there is >25% NOE between H-8′ and H-10′, only 12% NOE between H-8′ and H-10, and none between H-10 and H-10′. In **2** there is an almost equal NOE of 10−15% among all three protons, namely, H-8′ and H-10′, H-8′ and H-10, and H-10 and H-10′.

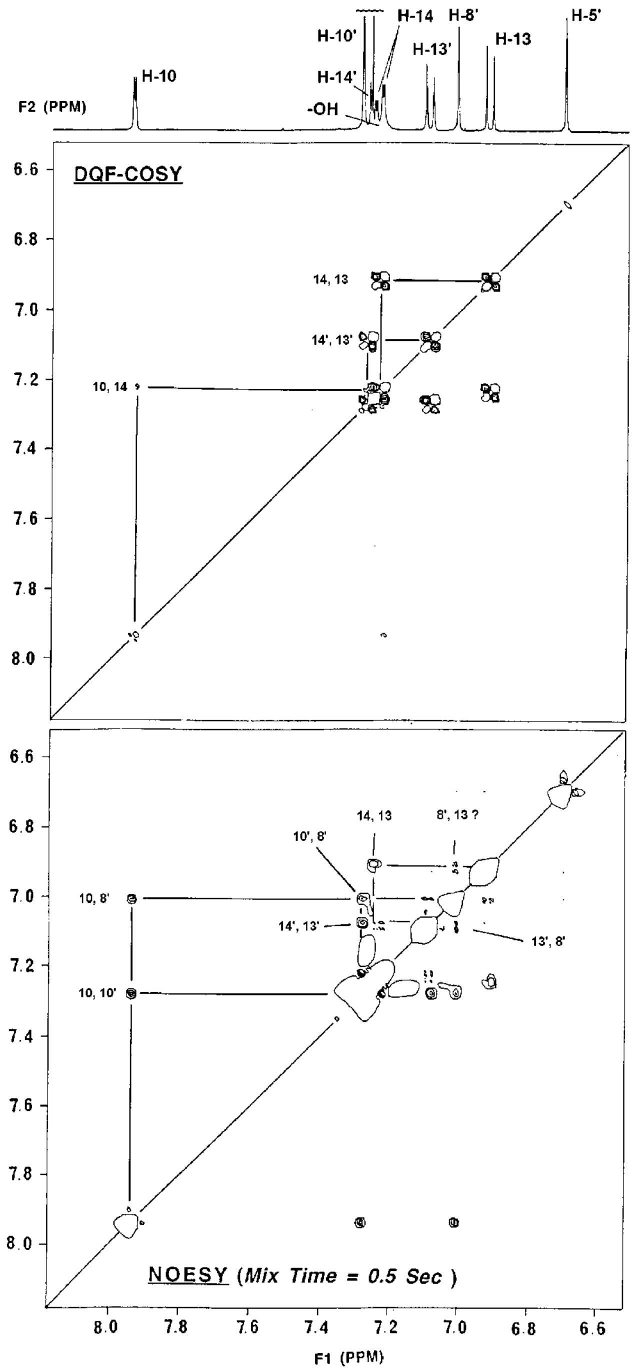

Figure 2. Expansion of the DQF-COSY and NOESY spectra ($CDCl_3$, 25 °C, NOESY mix time 0.5 s) of **1**.

An examination of the above experimental data clearly indicates that the largest NOE interactions among the aromatic ring protons occur in **1**. They occur between H-8′ on ring C and H-10′ on ring F, thus making them very close neighbors in space. Furthermore, it is no coincidence that the 0.4 Hz long-range coupling of interest occurs only in **1**, and it is between the resonance of the same two protons, namely, H-8′ and H-10′. Now we combine these two experimental facts with the unusually low field ($\delta = 8.10$) occurrence of the H-8′ resonance in the tiliacorinine (**1**) spectrum and can then explain the occurrence of the unusual seven-bond long-range coupling in the following manner (Figure 3).

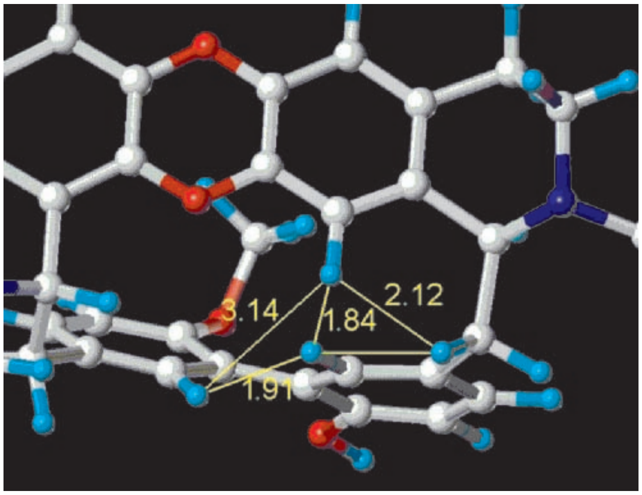

Figure 3. Energy-minimized structure of tiliacorinine (**1**) showing the distances in angstroms among the protons on rings C, D, E, and F. Note the short distance between H-8′ and H-10′ of 1.84 Å.

Although in both diastereoisomers H-8′ has an oxygen function as its *ortho* neighbor (Figure 1), the chemical shifts for H-8′ in the two compounds are very different. In **2**, H-8′ resonates at $\delta = 7.02$, a chemical shift position that is normal for the above-mentioned chemical environment, whereas in **1** the H-8′ signal is at $\delta = 8.10$, an unusually low downfield position. We attribute this downfield shift of 1.08 ppm in H-8′ to the long-range anisotropic deshielding effect of benzene ring F on H-8′ located on ring C. This deshielding action of the aromatic ring F on H-8′ suggests that H-8′ on ring C and H-10′ on ring F are located in an approximate 180° plane. This situation occurs only in **1** and not in **2**. Thus, when we combine the above information we can state that H-8′ of ring C and H-10′ of ring F are spatially very close and there is a strong possibility of an orbital overlap between H-8′ and H-10′. An orbital overlap of this type could very likely result in a through-space, spin−spin coupling between the two interacting protons.[4] To our knowledge, this is the first example of a through-space, seven-bond spin coupling between two aromatic protons that are located on two different benzene rings which are separated by two sp^3 carbon atoms.

Supporting Information Available: ^{1}H NMR spectrum at 100 MHz of **2** showing decoupling results; 1-D NOE measurements and solvent shifts ($CDCl_3$ vs C_6D_6); DQF-COSY data for **1**; NOESY data ($CDCl_3$, 25 °C, mix time 0.5 s) for **1**; expansion of the high-field region (2.2−4.4 ppm) of the DQF-COSY and NOESY spectra of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[4] Comments on the geometric requirements in proton−proton through-space couplings are noted in ref 1.