Simultaneous measurement of the magnitude and the sign of multiple heteronuclear coupling constants in small molecules

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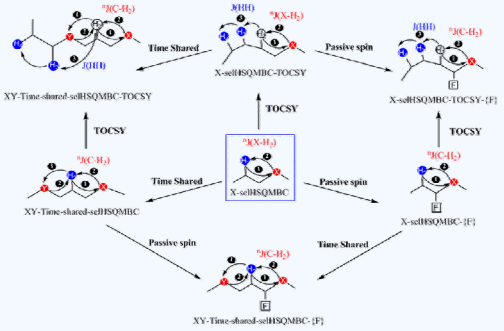
INTRODUCTION

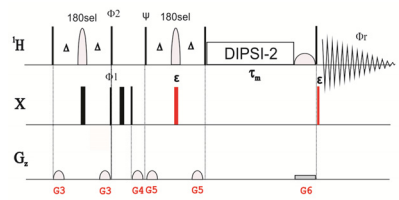
The determination of the magnitude of scalar heteronuclear coupling constants (J) has been established as an important step to be done for the structural characterization of small molecules in solution. In addition to the magnitude, the importance of the sign is capital to derivate theoretical and experimental correlations with structural parameters such as dihedral angles and pattern substitutions. Furthermore, the knowledge of the sign is mandatory for the proper measurement and use of residual dipolar couplings in molecules slightly oriented in anisotropic media.

We have recently reported a suite of powerful HSQMBC related experiments for the accurate measurement of proton-carbon coupling constants[1,2]. Here we make extensive these experiments to other heteronuclei than ^{13}C. We show that the magnitude and the sign of multiple heteronuclear coupling can be simultaneously measured from the analysis of a single cross-peak. We also discuss the enhanced effects to include TOCSY editing or the presence of passive spins and their complementarities with the IPAP and E.COSY strategies for the J coupling measurement. Finally, we propose also the use of Time-Shared methodology[3] which combine concatenated echo elements for simultaneous J(CH) and J(NH) coupling constants evolution, as well as simultaneous C,N chemical shift evolution during t1. In this way we can obtain simultaneous measurement of J(CH) and J(NH) in just a single NMR experiment.

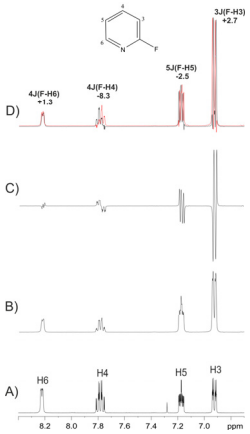


NMR PULSE SEQUENCES AND EXAMPLES

1D X-selHSQMBC-TOCSY



Pulse scheme of the 1D X-selHSQMBC-TOCSY. When the X red labelled pulses are applied, $^{n}J_{CH}$ evolves to in-phase (IP) and when they are omitted, anti-phase (AP) magnetization is obtained. Time-domain combination of theses IP and AP data afford separate α-, and β-spectra that allows the measurement of small $^{n}J_{CH}$ values. In addition, the experiment allows the measurement of the coupling sign since the TOCSY mixing time preserves the α/β–X spin-state information.



A) 1H NMR spectra B) IP and AP 1D X-selHSQMBC-TOCSY (X=19F) in fluoropyridine. D) α/β spin state selection for the accurate measurement of the sign and the magnitude of J(F-H)

2D X-selHSQMBC-TOCSY – {19F}

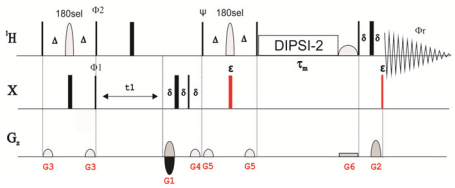
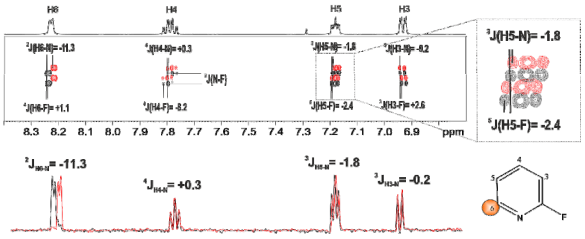
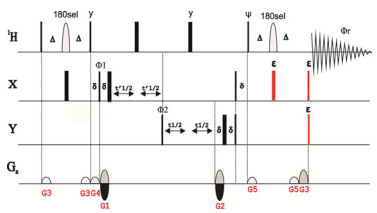


Figure shows the pulse sequence scheme of the 2D X-selHSQMBC-TOCSY-{19F}. The sequence is analog to 1D version but using coherence selection gradients. As explained for the 1D version, the IPAP selection is achieved in the acquisition dimension by recording the experiment with modified refocusing conditions. When applying these sequences to molecules having an abundant nucleus in their structures, additional heteroncular can be simultaneous measured. This is the case of 19F, where the corresponding J(HF) an the J(XF) coupling constants are also involved in the multiplet structure.

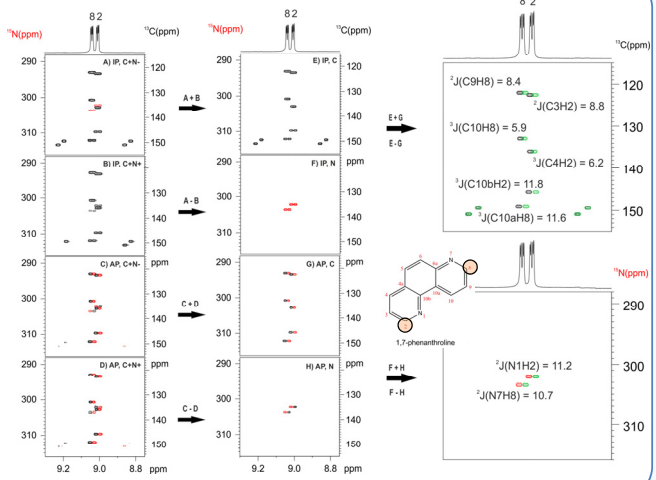


Expanded area showing α/β spectras corresponding to 2D 1H-15N selHSQMBC-TOCSY IPAP experiment after selective excitation of H6 proton of compound in 2-fluoropyridine. The passive 19F nucleus allows the determination of the sign and the magnitude of J(NF) and J(HF) from the relative E.COSY pattern generated along the indirect F1 dimension, while the sing and the magnitude of ^{n}J(NH) are measured from the relative displacement of the a-b spectra as it is shown in the 1D slices.

2D XY-Time-Shared-selHSQMBC



2D XY-TS-selhsqmbc pulse scheme. Examples are provided on 1,7-phenanthroline after selective excitation of H2 and H8 non-mutually coupled protons. A) IP data where Y=13C nucleus and X=15N nucleus has opposite phases. B) IP data where both 13C nucleus and 15N nucleus has the same phase. C) AP data where 13C nucleus and 15N nucleus has opposite phases. D) AP data where both 13C nucleus and 15N nucleus has the same phase. E) IP data only showing 13C nucleus. F) IP data only showing 15N nucleus. G) AP data only showing 13C nucleus. H) AP data only showing 15N nucleus. I) α/β–spectra only showing 13C nucleus, and J) α/β–spectra only showing 15N nucleus



References

1.- Saurí, J.; Espinosa, F.; Parella, T. *A Definitive NMR Solution for a Simple and Accurate Measurement of the Magnitude and the Sign of Small Heteronuclear Coupling Constants on Protonated and Non-Protonated Carbon Atoms.* Angew.Chem. Int. Ed. Vol. *51*, **2012**, pag. 3919-3922.
2.- Gil, S.; Espinosa, J.F., Parella, T. *Accurate measurement of small heteronuclear coupling constants from pure-phase α/ß HSQMBC cross-peaks*. J. Magn. Reson. Vol 213, **2011**, pag. 145–150.
3.- Parella, T.; Nolis, P. *Time Shared NMR experiments*. Conc. Magn. Reson. Vol 36A, **2010**, pag. 1-23.

Conclusion

In summary, it has been shown that the application of the selHSQMBC experiments can provide multiple information from a single experiment. In addition to the measurement of the existing proton-carbon coupling constants, it has been shown that the sign and the magnitude of different homonuclear and heteronuclear coupling constants can be measured with high simplicity from the single analysis of 2D cross-peaks.