Journal of Magnetic Resonance 236 (2013) 66–69

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Efficient and fast sign-sensitive determination of heteronuclear coupling constants

Josep Saurí, Pau Nolis, Teodor Parella *

Servei de Ressonància Magnètica Nuclear, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Barcelona, Spain

ARTICLE INFO

Article history:
Received 26 July 2013
Revised 16 August 2013
Available online 3 September 2013

Keywords:
Heteronuclear coupling constants
IPAP
HSQMBC-TOCSY
Sign of coupling constants

ABSTRACT

Two complementary 1D NMR approaches for the fast and easy determination of the magnitude and the sign of heteronuclear *J*(XH) coupling constants are proposed: The *Up&Down* technique relies on the direct analysis of anti-phase multiplets whereas the *Left&Right* technique is based on the relative displacement between separate IPAP components.

1. Introduction

The determination of the magnitude of heteronuclear spin–spin coupling constants (*J*) plays a fundamental role in the structural and conformational characterization of organic and organometallic molecules in solution [1]. Unfortunately no much attention has been paid to the determination of the positive/negative sign of a coupling [2], and this is essential to derive theoretical and experimental correlations with structural parameters such as dihedral angles, pattern of bonds connecting the coupling nuclei, pattern substitutions along the coupling pathway and others. The theoretical calculation of coupling constants has become an important tool for the interpretation of experimentally determined data, and also for the prediction of coupling constants that are not available experimentally. Specifically, the knowledge of the sign is mandatory for the proper measurement and use of residual dipolar coupling constants (RDCs) in molecules weakly oriented in anisotropic media [3] or to get more insight about the through-bond and through-space contributions in hydrogen-bonding interactions [4].

Herein we introduce NMR methodologies that address some remaining challenges in the measurement of heteronuclear *J*(HX) coupling constants: (i) the general application on any type of high (^{31}P and ^{19}F are 100%), medium (^{119}Sn (8.6%), ^{77}Se (7.6%...)) or low natural-abundance (^{13}C (1.1%), ^{15}N (0.3%)) ½-spin NMR heteronuclei; (ii) the measurement of small *J* values, including couplings between remote spins separated for more than the conventional two- and three-bond connectivities; (iii) the *J* measurement on multiplets with different pattern complexity; and (iv) special emphasis for the easy determination of the relative *J* sign. Many small molecules only contain a single *X* heteronucleus of interest, and therefore it could become more convenient to acquire the corresponding spectra in a 1D mode, improving simplicity, resolution and data collection speed up.

2. Results and discussion

Fig. 1 shows two related approaches, referred to Up&Down (U&D) and Left&Right (L&R) methods, for the fast, easy and accurate determination of *J*(HX). They are based on a family of HSQMBC experiments that have been proposed to determine small proton–carbon coupling constants [5–7]. All these experiments use selective ^{1}H refocusing to ensure the absence of any HH modulation, making the experimental extraction of *J* extremely easy from the direct analysis of pure-phase signals. In the U&D-technique, a ^{1}H–^{1}H TOCSY transfer is inserted into the last zz-period of the basic HSQMBC pulse train to extend the measurement to other protons belonging to the same spin system (Fig. 1A). The duration of the TOCSY transfer period can be optimized for each spin system under study as usual. The resulting multiplets will present pure in-phase (IP) patterns with respect to all HH couplings and anti-phase (AP) pattern with respect to the active HX coupling. This aspect of the data allows the extraction of the relative sign of *J*(XH) by comparing the relative up/down or down/up phase between multiplets because the α/β spin-state of the heteronucleus is not affected by the mixing TOCSY process. On the other hand, the magnitude of *J*(HX) can be measured analyzing the AP pattern in cases of well resolved

* Corresponding author.
E-mail address: teodor.parella@uab.cat (T. Parella).

1090-7807/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jmr.2013.08.013

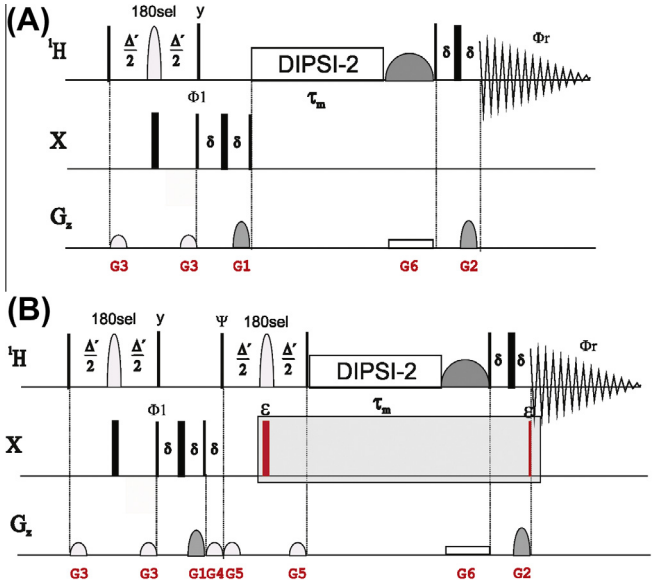

Fig. 1. (A) Non-refocused (*Up&Down* or *U&D*) and (B) refocused (*Left&Right* or *L&R*) versions of the 1D ^{1}H–X selHSQMBC-TOCSY experiment. The interpulse delays are optimized to $\Delta = \Delta' + p_{180} = 1/(2 * J_{XH})$, where p_{180} is the duration of the selective 180° ^{1}H pulse. The TOCSY transfer consists of a z-filtered DIPSI-2 pulse train of duration τ_m with an additional G6 gradient simultaneously applied to an adiabatic smoothed *CHIRP* pulse to remove unwanted ZQ contributions. In (B) Two independent IP and AP datasets are separately collected as a function of the pulses marked with ε: IP ($\Psi = y$ and ε = on) and AP ($\Psi = x$ and ε = off). Separate α/β data are obtained after time-domain addition/subtraction data (AP ± IP). A minimum two-step phase cycle is applied: $\phi_1 = x, -x$ and $\phi_{rec} = x, -x$. The ratio between gradients (with a duration δ) G1:G2:G3:G4:G5:G6 were set to x:y:33:50:17:3, where $x/y = \gamma_H/\gamma_X$. Gradients G1 and G2 are used for coherence pathway selection and they can be omitted when working with high-abundant nuclei. The experiments can be also run in 2D mode. See details on pulse sequence timing of these non-gradient selected 1D and 2D experiments in the Supporting information.

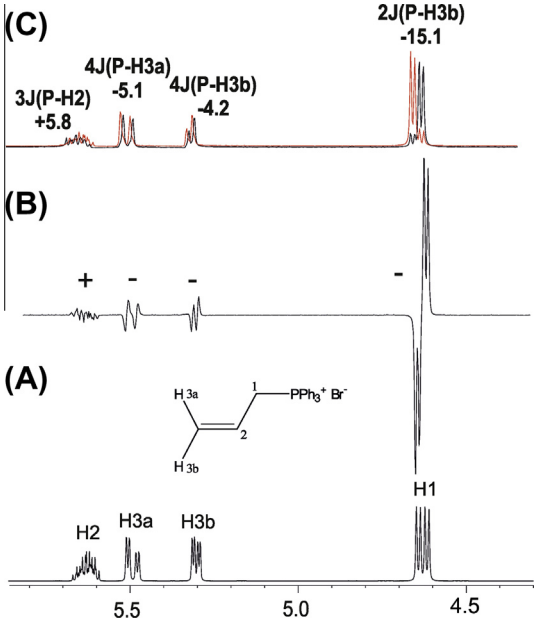

Fig. 2. 1D ^{1}H–^{31}P (B) U&D and (C) L&R spectra of 0.1 M allyltriphenylphosphonium bromide (**1**) in $CDCl_3$ acquired with the pulse sequences of Fig. 1A and 1B, respectively, without gradient coherence selection (see Fig. S1 in the Supporting information). The H1 proton was selectively excited with a 20 ms Gaussian-shaped 180° ^{1}H pulse and the inter-pulse delay and mixing times were optimized to 60 ms and 40 ms, respectively. 4 scans were collected with a relaxation delay of 1 s, giving an experimental time of only 16 s for each 1D spectrum.

multiplets or using a fitting procedure. Importantly, the intensity of a relayed H3–X signal does not depend of the J(H3–X) value but the cumulative J(H2–X) + J(H2–H3) pathway in the form of $2H_{3y}X_z\sin(\pi J_{H2X}\Delta)\cos(\pi J_{H2H3}\tau_m)$, and therefore small J(H3–X) values can be efficiently measured whenever TOCSY transfer is sufficiently effective.

Fig. 1B shows the refocused L&R version where IPAP selection is achieved by recording the experiment twice with modified refocusing conditions: when the X pulses marked with ε are applied, J(HX) is refocused to IP nature prior to acquisition whereas that AP magnetization is retained if they are omitted. Time-domain IP ± AP data combination followed by a conventional Fourier transformation afford the separate α- and β-spectra that allow the measurement of small J(HX) values by analyzing their relative signal frequency displacement. The sense of this displacement also provides the relative sign of J(HX) although that of a reference peak is needed to assign the absolute positive/negative value.

For low-abundance heteronuclei, the use of the G1 and G2 gradients for coherence selection (G1:G2 = γ_H/γ_X) is required to obtain high-quality U&D and L&R spectra. For high-abundance nucleus, such as ^{19}F or ^{31}P, gradients are not really needed, rendering the pulse sequences much more simple and sensitive (see Fig. S1 in the Supporting information for the corresponding pulse timing). In all cases, only H–X couplings that can be measured from a single 1D measurement are for those protons which are part of the same sequence of coupled protons as the selectively excited proton.

Several examples on standard molecules are shown here to illustrate the main features of the proposed experiments. For instance, although the magnitude of proton–phosphorus coupling constants, J(HP), can often be measured directly from the conventional ^{1}H multiplets or from simplified multiplets obtained from equivalent ^{31}P-decoupled 1D proton spectra of organophosphorus

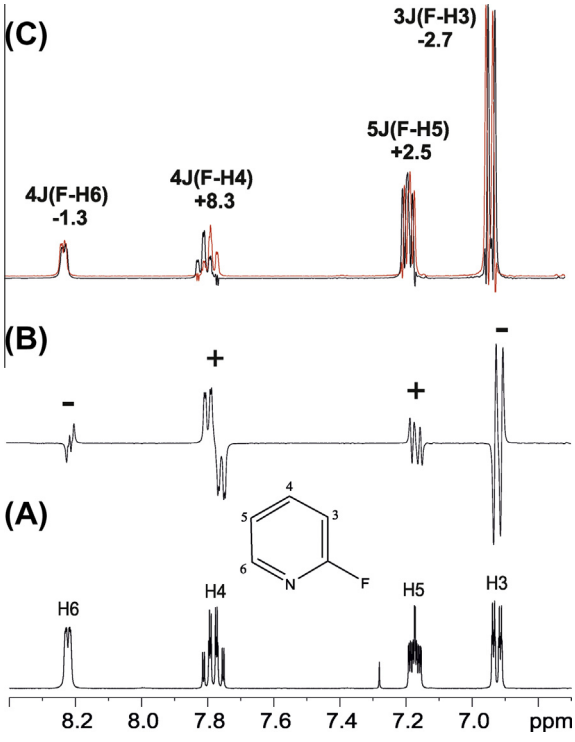

Fig. 3. 1D ^{1}H–^{19}F (B) U&D and (C) L&R spectra of 0.1 M 2-fluoropyridine (**2**) in $CDCl_3$ acquired with the pulse sequences of Fig. 1A and 1B, respectively, without gradient coherence selection. The H3 proton was selectively excited with a 20 ms Gaussian-shaped 180° ^{1}H pulse and the inter-pulse delay and mixing times were optimized to 60 ms and 40 ms, respectively. 4 scans were collected with a relaxation delay of 1 s, giving an experimental time of only 33 s for each 1D spectrum.