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Article

Ultrahigh-Resolution Homo- and Heterodecoupled ^{1}H and TOCSY NMR Experiments

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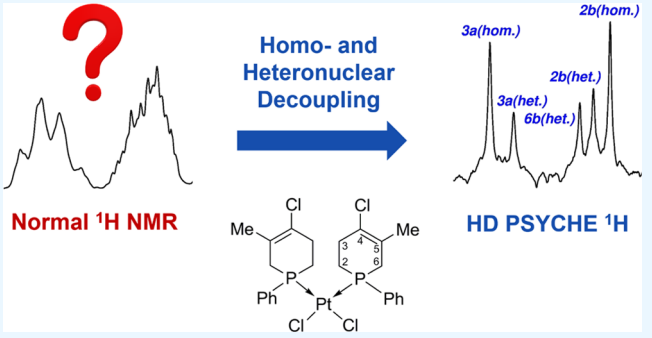
ABSTRACT: The original homonuclear decoupled (pure shift) experiments provide ultrahigh-resolution ^{1}H spectra of compounds containing NMR-active heteronuclei of low natural isotopic abundance (e.g., ^{13}C or ^{15}N). In contrast, molecules containing highly abundant heteronuclei (like ^{31}P or ^{19}F) give doublets or a multiple of doublets in their homonuclear decoupled spectra, depending on the number of heteronuclear coupling partners and the magnitude of the respective coupling constants. In these cases, the complex and frequently overlapping signals may hamper the unambiguous assignment of resonances. Here, we present new heteronuclear decoupled (HD) PSYCHE ^{1}H and TOCSY experiments, which result in simplified spectra with significantly increased resolution, allowing the reliable assessment of individual resonances. The utility of the experiments has been demonstrated on a challenging stereoisomeric mixture of a platinum−phosphine complex, where ultrahigh resolution of the obtained HD PSYCHE spectra made the structure elucidation of the chiral products feasible. HD PSYCHE methods can be potentially applied to other important ^{31}P- or ^{19}F-containing compounds in medicinal chemistry and metabolomics.



INTRODUCTION

Characterization of molecular structure is an essential step in many chemical research projects in both academic and industrial environments. Nuclear magnetic resonance (NMR) spectroscopy is one of the main techniques established for this purpose.[1] Sensitivity and resolution are key features for analytical methods, in general, and NMR spectroscopy, in particular. In the last two decades, the sensitivity and resolution of NMR experiments have significantly increased due to the two major reasons. Outstanding improvements in hardware, such as introduction of higher magnetic fields, cryogenically cooled probes, progresses in electronics, on the one hand, and pulse sequence developments, on the other hand, are responsible for considerable enhancements. From the NMR methodological point of view, the limited resolution can be increased by multidimensional experiments (optionally combined with nonuniform sampling (NUS))[2−4] and/or by suppressing undesired interactions such as *J*-couplings.[5,6] Signal overlaps are present most often in ^{1}H spectra due to the limited ^{1}H chemical shift range (~10−15 ppm), on the one part, and from extensive signal splittings caused by proton−proton couplings, on the other. Over the last decade, there has been a revival in the field of broadband homonuclear decoupling (also known as pure shift, PS) NMR,[7−9] which collapses multiplets into singlets by suppressing proton−proton *J*-couplings, leading to simplified ^{1}H spectra with increased resolution. Substantial efforts have been recently made to pave the way for the routine application of pure shift experiments in the structural characterization of organic molecules[10−15] and their complex mixtures in metabolomics.[16−20] However, in the case of compounds containing NMR-active heteronuclei in high abundance (e.g., ^{19}F, ^{31}P with 100% natural abundance), the homonuclear decoupled experiments provide ^{1}H spectra, in which proton sites coupled to the NMR-active heteronucleus give a doublet or multiple of doublets (when more than one heteronuclear coupling partner exists) split by the relevant $^{n}J_{HX}$ couplings.[21,22]

During our previous structural studies on phosphines and their transition-metal ion complexes,[23−25] we faced great challenges due to the occurrence of multiple ^{1}H−^{1}H and ^{1}H−^{31}P couplings in the ^{1}H NMR spectra, making assignment of individual resonances and measurement of coupling constants difficult or even impossible. Organophosphorus compounds are traditionally applied as ligands of transition-metal complexes in homogeneous catalytic reactions, such as hydrogenations or hydroformylations,[26−28] and their application in medicinal chemistry (e.g., Remdesivir)[29] also increased significantly in the last few years.[30,31] Despite the large number

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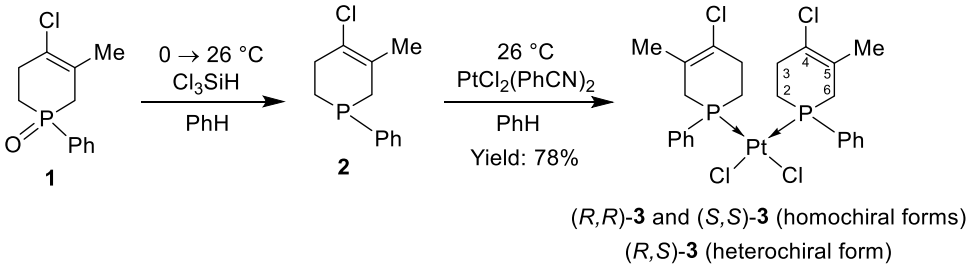
Scheme 1. Synthesis[24,35] of the 4-Chloro-1-phenyl-5-methyl-1,2,3,6-tetrahydrophosphinine−Platinum Complex (3) Investigated in This Study



of organophosphorus compounds reported in the literature, their structure verification is often challenging because of their complex ^{1}H NMR spectra with severely overlapping proton multiplets due to the pertinent multiple (^{1}H−^{1}H, ^{1}H−^{31}P) couplings. In the case of transition-metal complexes incorporating P-stereogenic ligands, the chemical syntheses may lead to diastereomeric mixtures, further complicating the characterization of the isolated products.[23,24,32] To circumvent these difficulties, we have designed novel one-dimensional (1D) ^{1}H and two-dimensional (2D) ^{1}H−^{1}H TOCSY NMR experiments with homo- and heteronuclear decoupling to make structure elucidation of this important class of compounds simpler, more accurate, and more reliable.

RESULTS AND DISCUSSION

Among the different approaches available for homonuclear decoupling, the PSYCHE (Pure Shift Yielded by Chirp Excitation) method[33,34] was chosen as a starting point because of its robustness and general applicability for compounds with various spin systems. We applied the PSYCHE ^{1}H experiment[33] to the platinum−phosphine complex (**3**) prepared from 1,2,3,6-tetrahydrophosphinine oxide (**1**) (Scheme 1) in two steps involving deoxygenation and complexation,[24,35] as it has an extremely complicated ^{1}H NMR spectrum for the P-heterocyclic region (Figure 1c) due to the similar chemical environment of the methylene groups and also the presence of various $^nJ_{HH}$ and $^nJ_{HP}$ couplings. Moreover, the chemical synthesis led to an inseparable mixture of stereoisomers (Scheme 1),[24,35] making the NMR assignment for structure verification unfeasible. As seen in Figure 1b, the resonance signals in the PSYCHE ^{1}H spectrum got simplified by suppressing proton−proton *J*-couplings; however, the signals of protons coupled to the ^{31}P nuclei still split with the pertinent $^nJ_{HP}$ couplings. Therefore, this homonuclear decoupled ^{1}H experiment can be used for the determination of the $^nJ_{HP}$ coupling constants, as demonstrated earlier.[22] Nevertheless, in routine operations, the main objective is typically the unambiguous NMR assignment for structure verification of the given product, which is still hampered in this particular case by the undesired signal splittings and overlaps (Figure 1b).

To eliminate all ^{1}H−^{31}P scalar couplings as well, we modified the standard PSYCHE sequence by incorporating a phosphorus inversion (180°) pulse simultaneously with the nonselective proton 180° pulse, as shown in the scheme of heterodecoupled (HD) PSYCHE pulse sequence (Figure 2). The combination of ^{1}H and ^{31}P nonselective inversion pulses with the PSYCHE element including a weak field gradient under a pair of small-flip-angle, swept-frequency Chirp pulses results in the refocusing of the evolution of unwanted homo- and heteronuclear couplings at the midpoint of the data acquisition period. In parallel, the sequence allows the continuous evolution of the proton chemical shifts. As in the standard PSYCHE experiment,[33] free induction decay (FID) is collected in chunks (1/sw1) of data, with a duration (typically 10−25 ms) short on the time scale of *J* evolution. Prior to regular Fourier transformation, a pseudo-1D data set (interferogram) with negligible homonuclear *J* modulation is constructed by concatenating all the data chunks recorded.

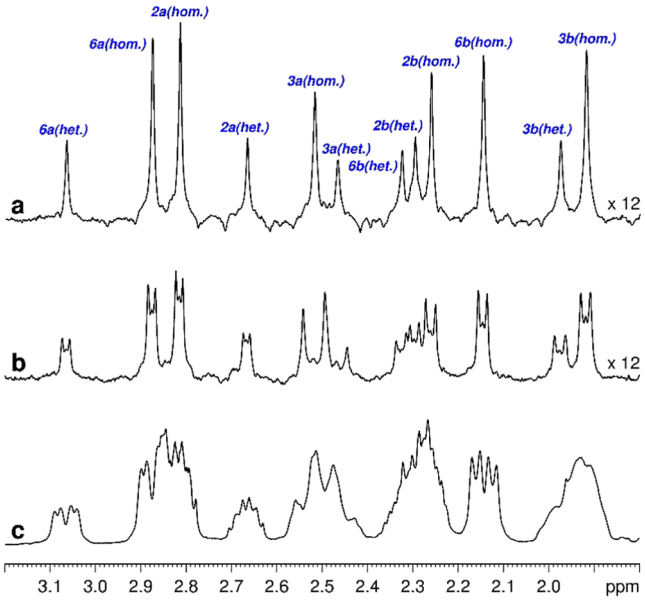


Figure 1. High-field region of HD PSYCHE (a), PSYCHE (b), and regular (c) ^{1}H NMR spectra obtained for a stereoisomeric mixture of platinum−phosphine complexes (**3** in Scheme 1). Resonance assignment is indicated above the HD PSYCHE spectrum (a), where het. and hom. abbreviations in parenthess stand for heterochiral and homochiral forms of the platinum−phosphine complex investigated. Intensities of HD PSYCHE (a) and PSYCHE (b) spectra are scaled up by 12 compared to the regular ^{1}H spectrum (c) for better visualization.

The complexity of the regular ^{1}H NMR spectrum of the reaction product, as seen in Figure 1c, makes signal assignments virtually impossible. In contrast, these complex multiplets got simplified by collapsing into singlets in the homo- and heterodecoupled HD PSYCHE spectrum depicted in Figure 1a. Consequently, the spectral resolution is dramatically increased, with all resonance signals completely separated from each other. Thus, the HD PSYCHE spectrum explicitly sheds light on the fact that multiple forms of the platinum−phosphine complex (Scheme 2) are generated in the reaction in Scheme 1. Integration of the two series of signals in

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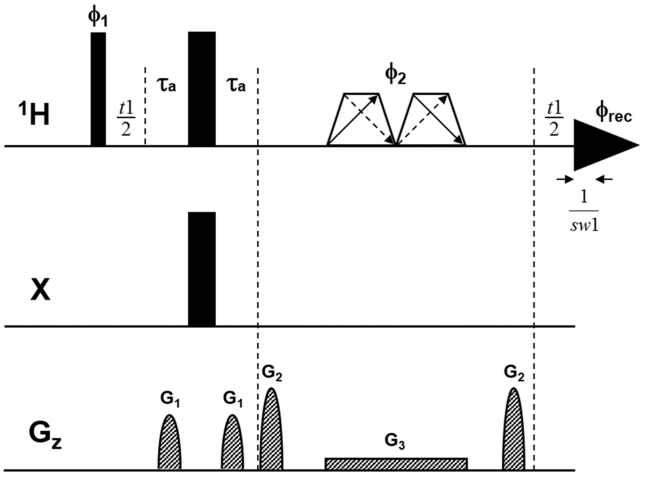


Figure 2. Pulse sequence scheme of the heteronuclear decoupled (HD) PSYCHE ^{1}H NMR experiment. Narrow and wide filled bars correspond to 90° and 180° pulses, respectively, with phase x unless indicated otherwise. Small-flip-angle (β), double-frequency-swept CHIRP pulses are shown as trapezoids with double diagonal arrows. Pulse phases are $\phi_1 = x, -x$; $\phi_2 = x, x, y, y, -x, -x, -y, -y$; and $\phi_{rec} = x, -x, -x, x$. Delay τ_a is equal to $1/(4 \times \text{sw1})$. Coherence selection gradient pulses (G_1 and G_2) are set to 49 and 77% of maximum gradient strength (50 G/cm), respectively. Sine bell-shaped gradient pulses of 1 ms duration are utilized, followed by a recovery delay of 1 ms. The weak magnetic field gradient (G_3) used under the CHIRP pulses is adjusted for 1.8% of maximum gradient strength.

the HD PSYCHE spectrum shows that the more intense signals belong to the homochiral forms (two enantiomers), while the less intense ones belong to the heterochiral form (one diastereomer). The sensitivity price to pay for using PSYCHE decoupling is about one order of magnitude, but some signal intensities are regained by eliminating the multiplet structures of resonances.

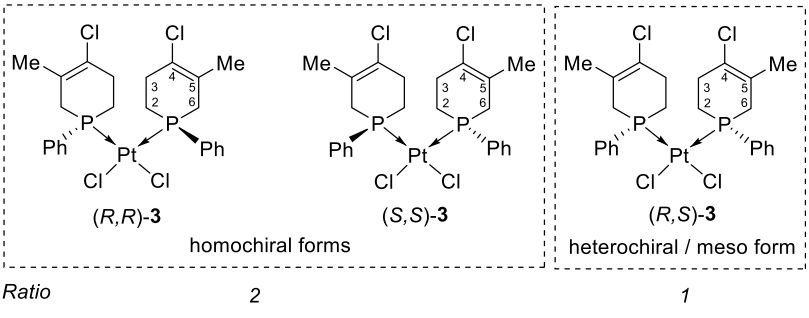
For the complete NMR assignment of platinum−phosphine complexes, especially if we have stereoisomeric mixtures in hand, 2D correlation experiments are essential. However, in the regular 2D homonuclear spectra, we would face the same problems as in 1D ^{1}H. Thus, we have also designed 2D homo- and heterodecoupled (HD) PSYCHE TOCSY pulse sequences. PSYCHE homonuclear decoupling was previously introduced to both dimensions (F1 and F2) of the 2D TOCSY experiment.[36] We have modified these PSYCHE TOCSY pulse sequences to achieve heteronuclear decoupling in both dimensions as well (Figures 3 and 4). Heterodecoupling in F1 was achieved by a ^{31}P inversion pulse properly placed in the sequence, while in the F2 dimension composite, ^{31}P pulse decoupling (CPD) was employed during acquisition. As a result, we have developed an F1-homo- and heterodecoupled and F2-heterodecoupled (Figure 3) and an F1-heterodecoupled and F2-homo- and heterodecoupled (Figure 4) TOCSY experiment.

The new methods were applied to the challenging stereoisomeric mixture of platinum−phosphine complexes (Scheme 2). As illustrated in Figure 5a, the broad multiplets due to several ^{1}H−^{1}H and ^{1}H−^{31}P couplings cause serious overlaps in the regular TOCSY spectrum. In contrast, much cleaner 2D ^{1}H−^{1}H correlation maps with enhanced resolution were produced by both variants of the HD PSYCHE TOCSY experiments (Figure 5b,c). Either of these spectra clearly separates the correlation signals of the homo- and heterochiral forms of the product, allowing unambiguous assignment of proton resonances, as given above in the HD PSYCHE ^{1}H spectrum (Figure 1a). The F1-PSYCHE method has the advantage that an additional pseudodimension is not required to achieve decoupling. In contrast, the F2-homodecoupled experiment relies on chunking (interferogram-based) acquisition, similar to the 1D PSYCHE experiment. In practice, the F1-PSYCHE experiment (Figure 5b) was realized in 2 h 22 min measurement time, while F2-PSYCHE TOCSY required 16 h 24 min of experiment time (Figure 5c). Moreover, from the F1-homo- and heterodecoupled and F2-heterodecoupled PSYCHE TOCSY spectrum, ^{1}H−^{1}H coupling constants can be also determined with high resolution when needed. By applying covariance processing for either of HD PSYCHE TOCSY spectra, completely decoupled 2D TOCSY correlation maps with ultrahigh resolution could be obtained, as illustrated in Figure 5d. The well-resolved singlet peaks of these spectra make the application of automatic peak-picking and NMR assignment algorithms feasible to speed up the structure elucidation procedure.

CONCLUSIONS

In conclusion, we have developed HD PSYCHE 1D ^{1}H and 2D TOCSY methods via introducing heteronuclear decoupling to obtain pure shift spectra in the case of compounds containing an NMR-active heteronucleus with significant abundance (e.g., ^{31}P with 100% natural abundance). The new homo- and heteronuclear decoupled experiments were applied to a stereoisomeric mixture of a platinum−phosphine complex, a case wherein NMR structure elucidation was not feasible based on regular spectra with overlapping multiplets due to ^{1}H−^{1}H and ^{1}H−^{31}P couplings. With the aid of the fully decoupled pure shift experiments presented here, unambiguous

Scheme 2. Homo- and Hetetochiral Forms of the Platinum−Phosphine Complex (3) Were Formed in a Ratio of ca. 2:1 in the Synthesis,[24,35] Which Was Verified by the New HD PSYCHE Experiment



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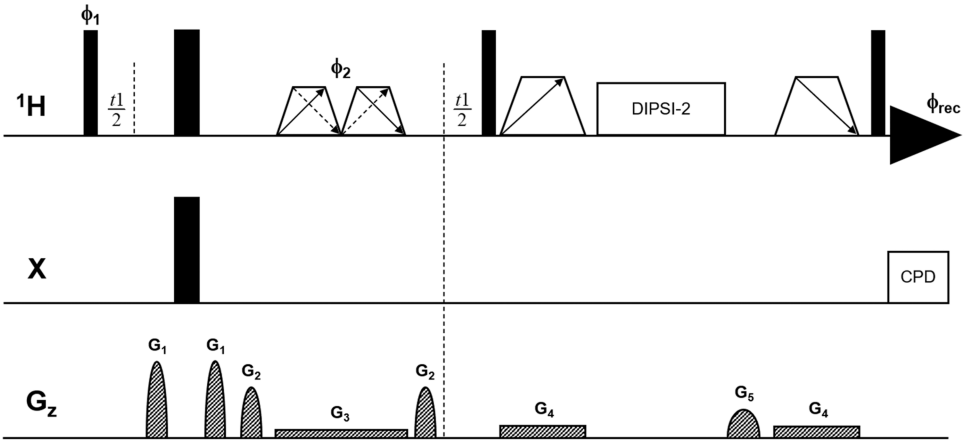

Figure 3. Pulse sequence scheme of the F1-homo- and heterodecoupled and F2-heterodecoupled PSYCHE TOCSY experiment. Narrow and wide filled bars correspond to 90° and 180° pulses, respectively, with phase x unless indicated otherwise. Low-flip-angle (β), double-frequency-swept CHIRP pulses are shown as trapezoids with double diagonal arrows in the t_1 evolution period. Frequency-swept CHIRP pulses for zero quantum suppression[37] are illustrated as trapezoids with a single diagonal arrow. Pulse phases are $\phi_1 = x, -x$; $\phi_2 = x, x, y, y, -x, -x, -y, -y$; and $\phi_{rec} = x, -x, -x, x$. Phase-sensitive detection is achieved according to the TPPI protocol. The DIPSI-2 sequence is used for TOCSY mixing. Coherence selection gradient pulses (G_1 and G_2) are set to 77 and 49% of maximum gradient strength (50 G/cm). Sine bell-shaped gradient pulses of 1.5 ms duration are utilized, followed by a recovery delay of 500 μs during the t_1 evolution period. The weak magnetic field gradient (G_3) used under the CHIRP pulses of the PSYCHE block is adjusted for 1.5%. The purging gradient pulse (G_5) is set to 25%, typically with a 2.5 ms duration followed by a recovery delay of 500 μs. Weak magnetic field gradients (G_4) used under the frequency-swept CHIRP pulses for zero quantum suppression are adjusted for 4% of maximum gradient strength. The GARP sequence is used for heteronuclear composite pulse decoupling (CPD) during detection.

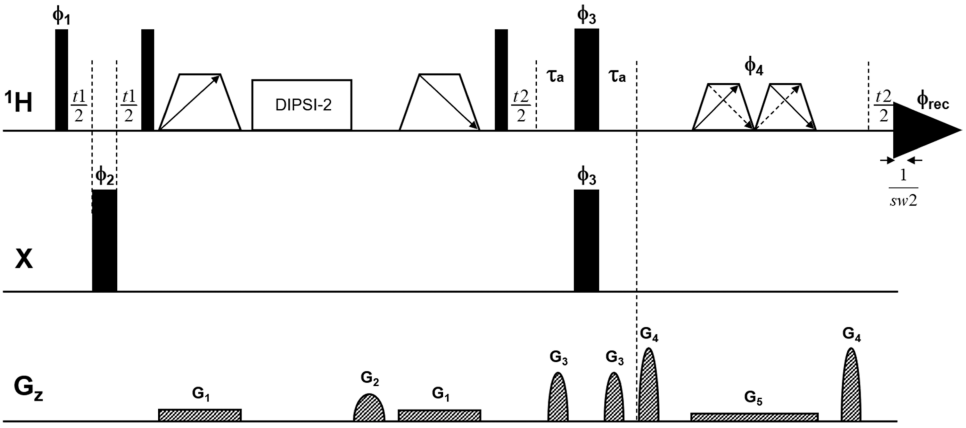

Figure 4. Pulse sequence scheme of the F1-heterodecoupled and F2-homo- and heterodecoupled TOCSY experiment. Narrow and wide filled bars correspond to 90° and 180° pulses, respectively, with phase x unless indicated otherwise. Frequency-swept CHIRP pulses for zero quantum suppression[37] are illustrated as trapezoids with a single diagonal arrow. Low-flip-angle (β), double-frequency-swept CHIRP pulses in PSYCHE element are shown as trapezoids with double diagonal arrows. Pulse phases are $\phi_1 = x, -x$; $\phi_2 = x, x, -x, -x$. $\phi_3 = x, x, x, x, x, x, x, x, y, y, y, y, y, y, y, y$; $\phi_4 = x, x, y, y, -x, -x, -y, -y$; and $\phi_{rec} = x, -x, -x, x, x, -x, -x, x, -x, x, x, -x, -x, x, x, -x$. Delay τ_a is equal to $1/(4 \times sw2)$. Phase-sensitive detection is achieved according to the TPPI protocol. The DIPSI-2 sequence is used for TOCSY mixing. Weak magnetic field gradients (G_1) used under the frequency-swept CHIRP pulses for zero quantum suppression are adjusted for 4% of maximum gradient strength (50 G/cm). Purging gradient pulse (G_2) is set to 25%, typically with a 2.5 ms duration followed by a recovery delay of 500 μs. Coherence selection gradient pulses (G_3 and G_4) are set to 49 and 77%, respectively. Sine bell-shaped gradient pulses of 1 ms duration are utilized, followed by a recovery delay of 1 ms. The weak magnetic field gradient (G_5) used under the pair of CHIRP pulses in the PSYCHE block is adjusted for 1.8% of maximum gradient strength.

NMR assignment of the challenging stereoisomeric mixture of a reaction product could be achieved. Phosphorus-containing compounds are important players not only in catalysis but also in medicinal chemistry and various biochemical processes, to mention nucleotides for example. Furthermore, fluorine-containing compounds, which are common and important drug candidates in modern pharmaceutical chemistry, raise similar challenges in ^{1}H NMR spectroscopy due to the 100% natural abundance of the ^{19}F NMR-active nucleus. It should be noted that an alternative solution for heteronuclear decoupling in the 1D PSYCHE ^{1}H experiment has been recently proposed,[38] which efficiently takes care of the large chemical shift and $^nJ_{HX}$ coupling range typical for ^{19}F-containing molecules. Thus, the widespread application of HD PSYCHE ^{1}H and TOCSY methods for NMR structure elucidation is envisioned in several fields of medicinal chemistry and metabolomics.

METHODS

All NMR experiments were performed on a Bruker Avance II 500 MHz spectrometer equipped with a 5 mm z-gradient BBI probe at 303 K. A sample of 30 mg from the stereoisomeric

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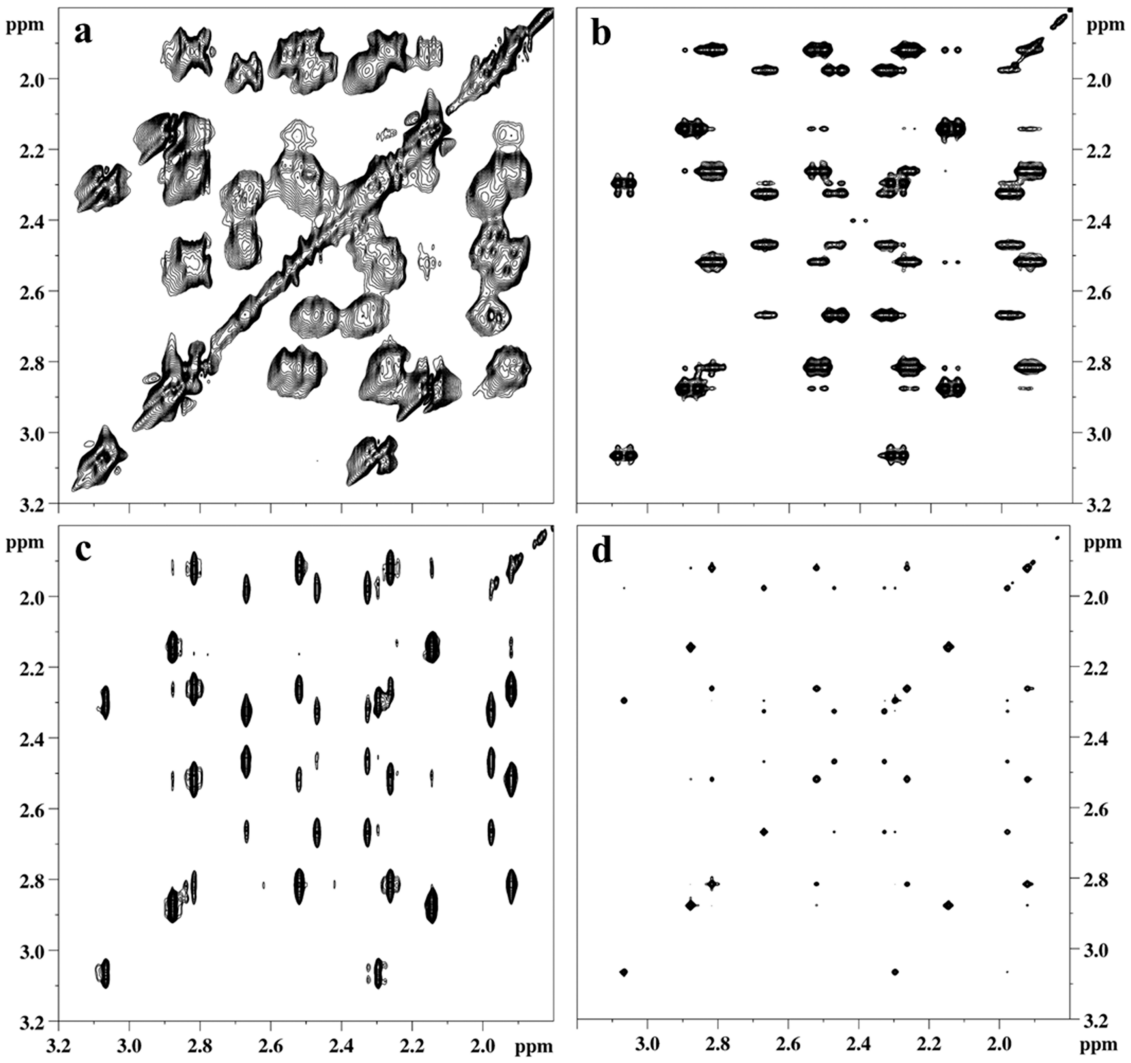

Figure 5. Comparison of regular (a), F1-homo- and heterodecoupled and F2-heterodecoupled (HD) PSYCHE (b), F1-heterodecoupled and F2-homo- and heterodecoupled (HD) PSYCHE (c), and covariance processed HD PSYCHE (d) ^{1}H−^{1}H TOCSY NMR spectra obtained for a stereoisomeric mixture of platinum−phosphine complexes (**3** in Scheme 2).

mixture of platinum−phosphine complexes (**3** on Scheme 2) dissolved in 500 μl of $CDCl_3$ was used for the NMR measurements. A pair of double-frequency-swept, 15 ms long CHIRP pulses of net flip angle β = 24° was used in the PSYCHE experiments. The regular ^{1}H NMR spectrum in Figure 1c was recorded with a spectral width of 11.0346 ppm, 16384 total data points, a relaxation delay of 1.5 s, and 16 scans with an overall experimental time of 1 min. The HD PSYCHE and PSYCHE ^{1}H spectra in Figure 1a,b were acquired with a spectral width of 9.9774 ppm, 32 t_1 increments (i.e., number of FID chunks), a 20.04 ms duration of FID chunks, a relaxation delay of 1.5 s, and 4 scans with an overall experimental time of 8 min. All ^{1}H−^{1}H TOCSY spectra in Figure 5 were recorded with a spectral width of 4.9887 ppm, 2048 total data points in the direct dimension, a relaxation delay of 1.5 s, and 40 ms DIPSI-2 mixing time. The regular ^{1}H−^{1}H TOCSY spectrum in Figure 5a was acquired with 400 total data points in the indirect dimension and 4 scans with an overall experimental time of 56 min. The F1-homo- and heterodecoupled and F2-heterodecoupled (HD) PSYCHE TOCSY spectrum in Figure 5b was recorded with 1024 total data points in the indirect dimension and 4 scans with an overall experimental time of 2 h 22 min. The F1-heterodecoupled and F2-homo- and heterodecoupled (HD) PSYCHE TOCSY spectrum in Figure 5c was acquired with 16 t_2 increments (i.e., number of FID chunks), a 20.04 ms duration of FID chunks, 400 total data points in the indirect dimension, and 4 scans with an overall experimental time of 16 h 24 min.

Bruker TopSpin computer software (version 2.1 and 3.6.2) was used for processing of NMR spectra including zero-filling, exponential (for 1D) or cosine square (for TOCSY) apodization, Fourier transformation, and phase and baseline correction. Before regular Fourier transformation, (HD) PSYCHE ^{1}H and F2-homo- and heterodecoupled PSYCHE TOCSY raw data sets were processed with a Bruker AU program (*pshift*) to reconstruct the 1D and 2D interferograms, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06102.

Pulse sequence codes for Bruker spectrometers (PDF)

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Notes

The authors declare no competing financial interest.

During the finalization of current manuscript, a similar approach to our 1D heterodecoupled PSYCHE ^{1}H NMR method was published by Mycroft et al.[38]

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