J. Am. Chem. Soc. 1995, 117, 2927−2928

Hetero-NMR Enhancement via Parahydrogen Labeling

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Received September 21, 1994

Homogeneously catalyzed hydrogenation reactions lead to strong nuclear spin polarization effects in ^{1}H NMR spectra, if parahydrogen (p-H$_2$) is used instead of normal hydrogen (n-H$_2$, i.e., H$_2$ in thermal equilibrium). This PASADENA[1] effect results from the breakdown of the high p-H$_2$ symmetry during the hydrogenation, if the p-H$_2$ protons are transferred pairwise to maintain their spin correlation. Also termed parahydrogen-induced polarization (PHIP)[2] or "parahydrogen labeling", this method with its signal enhancement (SE) has already been used for *in situ* NMR detection of short-lived reaction intermediates during organometallic-catalyzed hydrogenations, for mechanistic and kinetic investigations,[3−9] and for polarization transfer to hetero nuclei also in conjunction with INEPT experiments.[7,8]

Indeed, the PASADENA effect is not restricted to protons, as has been postulated[1,4] and demonstrated before[7,8] for ^{13}C and ^{31}P, albeit with SE < 10. We want to point out that much higher SE may result for such hetero nuclei, yielding almost *proton* sensitivity, if the system meets certain requirements. We want to highlight this for naturally abundant ^{13}C using the reaction in Scheme 1 as a characteristic example.

Figure 1shows the ^{13}C NMR spectrum of the hydrogenation product of acetylenedicarboxylic dimethyl ester (**I**), namely, of maleic acid dimethyl ester (**II**), detected after 20 s of reaction time, using just a single 90_x (^{13}C) pulse.

Previous INEPT+ experiments by Eisenberg[7,8] allow the transfer of nuclear spin polarization to hetero-nuclei, too, but result in a lower SE of the ^{13}C resonances and give rise to strikingly different polarization patterns of the proton-coupled ^{13}C multiplets as outlined in Figure 2.

To carry out the experiments, 5 mm NMR tubes equipped with a Teflon pressure valve were charged with 50 μL of **I**, 10 mg of the catalyst [Rh(cod)(dppb)(PPh$_3$)$_2$]BF$_4$ (Cat.), 0.8 mL of degassed acetone-d_6, and 3 bar of p-H$_2$ enriched over charcoal at 77 K to 50%.[9] The tubes were closed, shaken, and placed into the NMR probe at room temperature. After ca. 20 s the FID shown in Figure 1a was detected using a *single* 90_x (^{13}C) pulse. The appearance of this FID and the corresponding signal to noise ratio (S/N) of the ^{13}C signals is remarkable, since the concentration of **II** is <0.1 mol L^{-1}. For the system given here, the SE can be derived from the S/N by comparing the S/N value of the largest signal of the quartet at 166.2 ppm observed during the reaction to that corresponding to the equivalent product concentration as determined after the reaction.[7,8] In order to detect the carboxy group of 10 μL of product **II** with a S/N of 5 required 1850 scans, corresponding to 26 h of spectrometer time. Our *single-scan in situ* experiment yields in several experiments a S/N of up to 300 corresponding to a SE of 2580. To obtain an equivalent S/N after the reaction would require 6.7×10^6 scans and more spectrometer time accordingly. An additional heterodecoupling of the methoxy protons yields an increasing S/N of up to 800.

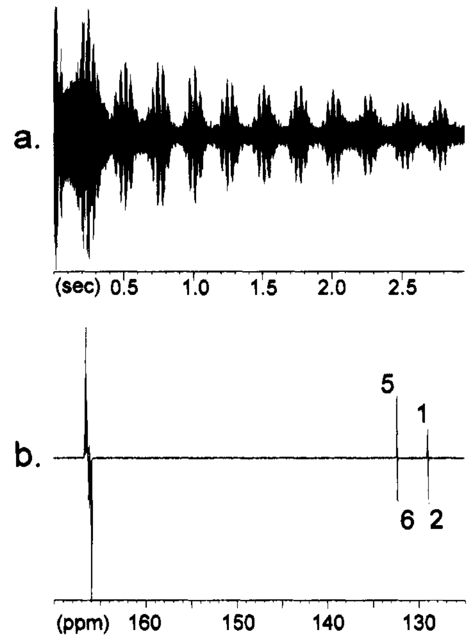
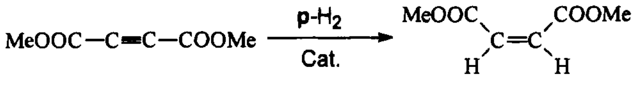


Figure 1. ^{13}C-PHIP spectrum of **II**: (a) single FID taken 20 s after starting the reaction of 50 μL of **I** with p-H$_2$. (b) FFT of spectrum a. The numbers relate to the transitions marked in Figure 3.

Scheme 1



I **II**

An INEPT pulse sequence[10] applied instead to this reacted sample results in a S/N of only 34 even after 7400 scans (Figure 2). Therefore, even the INEPT method would require 5.8×10^5 scans to yield a S/N equivalent to that of our single-scan experiment.

The ^{13}C signals of the methoxy groups of **II**, normally observable at 52.1 ppm, exhibit no significant SE, due to insufficient J coupling to the olefinic protons. Consequently, this leaves two different ^{13}C-containing isomers of **II** to be considered, namely, one containing the sequence ^{13}CO—^{12}CH=^{12}CH (i.e., the reaction product **IIa**), and the other ^{12}CO—^{13}CH=^{12}CH (reaction product **IIb**).

The transitions which dominate the spectra obtained either via ^{13}C-{^{1}H}-PHIP, ^{13}C-PHIP, INEPT, or the standard ^{13}C experiments are outlined in Figure 3.

Thereby it is assumed, neglecting the $^{3}J_{\mathrm{CH}}$ coupling of the carboxy carbon atom to the methoxy protons which leads to the splitting up into quartets, that the then remaining three-spin system of **IIa** can be regarded as an AA′X case.[11] This allows one to express the eigenstates as a product of symmetrized singlet (S) and triplet (T$_+$,T$_0$,T$_-$) functions for the AA′ part and the simple high-field functions α and β for the X part (Figure 3).

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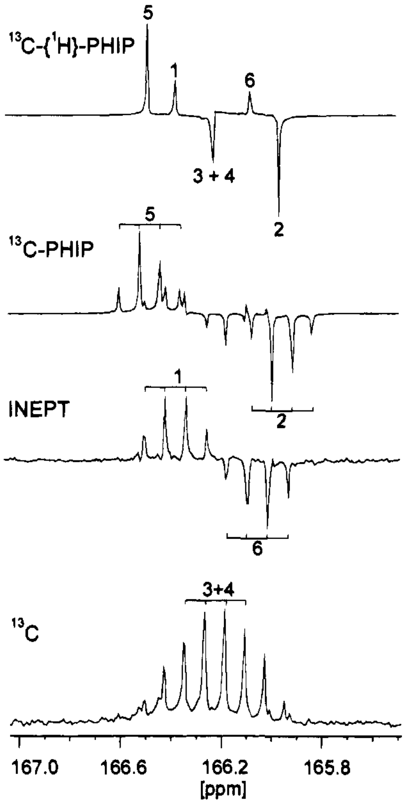

Figure 2. Zoom of CO resonance of **IIa** at 166.2 ppm obtained during the reaction using selective decoupling of the methoxy protons (^{13}C-{^1H}-PHIP); without decoupling (^{13}C-PHIP); ^{13}C spectrum of 10 μL of **II** after 926 scans when applying an INEPT pulse sequence ($1/4J = 0.019$ s) (INEPT); ^{13}C-spectrum of 100 μL of **II** after 3208 scans (^{13}C). The numbers relate to the transitions marked in Figure 3.

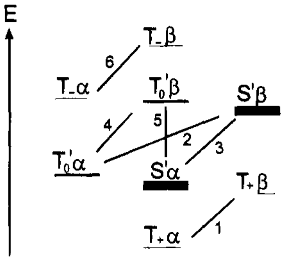

Figure 3. Simplified representation of the energy levels of ^{13}C-containing **II** as a three-spin system (i.e., when applying selective decoupling on the methoxy protons) and observable transitions for the ^{13}C nuclei.

Whereas the functions $T_{+}\alpha$, $T_{+}\beta$, $T_{-}\alpha$ and $T_{-}\beta$ are eigenfunctions and have 100% triplet symmetry with respect to the protons in the AA′ position, the other four functions are linear combinations of the related terms $S\alpha$, $S\beta$, $T_0\alpha$, and $T_0\beta$. For example, $T'_0\alpha$ means that this eigenfunction is a linear combination of the eigenstates $T_0\alpha$ and $S_0\alpha$ with a dominating triplet symmetry for the AA′ protons.

With respect to reaction product **IIa**, the former p-H_2 protons are transferred into the AA′ positions of this AA′X spin system and populate each eigenstate $S'\alpha$ and $S'\beta$ with a normalized probability of ca. 0.48, whereas $T'_0\alpha$ and $T'_0\beta$ are populated with a probability of only 0.02 each. Therefore, the ^{13}C-{^1H}-PHIP spectrum (Figure 2) shows the combination transitions 2 and 5 with a calculated transition probability of 0.16. Considering now the neglected coupling of the ^{13}CO carbon to the three methoxy protons, these transitions exhibit a dominating antiphase quartet (Figure 2; ^{13}C-PHIP).

In contrast, in a normal ^{13}C spectrum recorded in the absence of nuclear polarization, transitions 4 and 3 superimpose, i.e., they add and dominate the spectrum (Figure 2; ^{13}C). This is due to the transition probability, which is 1.92 for transitions 3 and 4 and 1.00 for 1 and 6. Consequently, these transitions are extremely sensitive for nonequal populations of the respective energy levels after hydrogen addition.

The ^{13}C-INEPT spectrum shown in Figure 2, however, reveals only the signals corresponding to transitions 1 and 6, because the possible transitions 3 and 4 cancel each other in antiphase.

One striking feature is that our ^{13}C-PHIP spectra do not reflect the theoretically expected equal spin population between the energy levels connected through transitions 1, 3, 4, and 6. Consequently, in both PHIP patterns additional signals can be detected labeled as 1, 3, 4, and 6 (Figure 2; ^{13}C-{^1H}-PHIP). The explanation for this is the contribution of time-dependent relaxation processes after initializing the hydrogenation reaction. Further experiments show that these transitions can be suppressed by minimizing the delay time between hydrogenation and aquisition.[12]

Turning now to reaction product **IIb**: The signals of the olefinic carbon atoms at 130.2 ppm (Figure 1b) can be explained assuming that **IIb** is an AA′X spin system, too. Here the former p-H_2 protons populate the eigenstates $S'\alpha$ and $S'\beta$ of **IIb** with a probability of 0.285, and $T'_0\alpha$ and $T'_0\beta$ with 0.215, which again leads to transitions 2 and 5. Furthermore, time-dependent dipolar coupling between the geminal ^{13}CH nuclei induces cross relaxation. The resulting nuclear Overhauser effect transfers population from $S'\beta$ and $T'_0\beta$ to $T_{+}\alpha$, and from $S'\alpha$ and $T'_0\alpha$ to $T_{-}\beta$; therefore, the transitions indicated as 1 and 6 in Figure 1b are additionally observable.

The degree of polarization of the hetero nucleus, here ^{13}C, is most effective if the former p-H_2 protons are transferred into positions which are chemically more or less equivalent, but where this hetero nucleus causes a breakdown of their symmetry by virtue of an asymmetric scalar coupling. Both reaction products **IIa** and **IIb** investigated here meet this requirement, which explains their impressive SEs. We have calculated the maximum degree of polarization for an AA′X-spin system which exhibit the following ratio of coupling constants:[13] $(J_{AX} - J_{A'X})/J_{AA'} = 8^{1/2}$.

Even if the two p-H_2 protons are transferred into different chemical environments associated with different chemical shifts, the hetero nucleus still experiences some degree of polarization, albeit less. Since differences of the chemical environment are insignificant in the absence of a magnetic field, however, the polarization efficiency for the hetero nuclei is especially pronounced if the reactions are carried out either in zero or very low magnetic fields, whereby the reaction products may be investigated at the high field of conventional NMR spectrometers.[12]

The experimental procedure discussed here is also suited for other heteronuclei, especially for the direct *in situ* NMR detection of scarcely abundant and of *low* γ nuclei, e.g., ^{29}Si, ^{15}N, ^{17}O, ^{109}Rh, etc. In order to distinguish the observed nuclei in parahydrogen-labeling experiments, we propose the use of the observed isotope as a prefix, here ^{13}C-PHIP.

Acknowledgment. Financial support was obtained from the Bundesministerium für Forschung und Technologie, Volkswagenstiftung, and Fonds der Chemischen Industrie, Frankfurt am Main. M.H. thanks the K.-Adenauer-Stiftung for a graduate fellowship.

Supplementary Material Available: ^1H and ^{13}C NMR data of **II** in acetone-d_6 at 200 MHz and intensitiy calculation of combination transistions 2 and 5 (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) The relative phases and intensities of the transitions reflect the corresponding populations of the energy levels of the nuclear spin system. The results of a detailed analysis of the dynamic processes leading to their selective population and depopulation will be published shortly.