

Screening Catalysts for the Catalytic Exchange of Hydrogen by Tritium Using Magnetic Labeling

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Summary:

Isotope labeling is an important method to evaluate drugs and compounds for agricultural use. Therefore, a fast and convenient method to selectively exchange hydrogen against non-radioactive deuterium or radioactive tritium in the final product is desirable. PHIP-NMR investigations of the influence of CO on the selective exchange of the geminal protons in styrene show that CO increases the efficiency of the selective exchange non-linearly and suppresses the hydrogenation of styrene to ethylbenzene.

Keywords:

Catalysis, NMR, Hydrogenation, Exchange reactions, Magnetic Labeling

1. Introduction

The use of isotopes, either stable or radioactive, as tracers for monitoring the metabolic fate of new drugs or compounds for agricultural use is of key significance.¹ In organic chemistry, replacing hydrogen by deuterium is a widely used labeling technique, whereas tritium serves as a radioactive

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tracer. The latter enables the application of very sensitive analytical methods to study the metabolic fate of drugs in an organism, for which purpose a radio-label is required at a specific, metabolically safe position in the molecule. In order to prepare specifically tritiated compounds, there are mainly two chemical methods:² Specific tritiations can either be achieved by direct chemical synthesis, starting from suitable precursors or via catalytic hydrogen isotope exchange in the final product. Since any "hot" synthesis requires special equipment, highly trained and experienced specialists, and laboratories certified for the required safety precautions in the handling of radioactive substances, this approach is costly and time-consuming. Furthermore, it generates a fair amount of radioactive waste. Therefore, labeling via catalytic exchange of hydrogen against tritium in the final product is attractive, since it typically requires only one step. This approach is efficient, i.e., fast and less expensive, but it is limited to easily exchangeable atoms, and the exchange has to occur in a very specific and reliable fashion. In this study, we show that to identify suitable homogeneous catalysts for this purpose, it is not necessary to use tritium or even deuterium; rather, magnetic labeling represents an attractive alternative.

The potential of using the spin isomers of dihydrogen, i.e., ortho- and parahydrogen, for magnetic labeling studies has been outlined before.^{3a} It has since been found that parahydrogen can be successfully used as a substitute for tritium in catalyst screening studies to identify suitable organometallic compounds which catalyze the exchange homogeneously.^{3b} The advantages of using a magnetic labeling technique instead of a radioisotope-based approach are obvious: it makes special handling required for radioactive isotopes obsolete and thereby speeds up the investigations, thereby reducing the costs even further. The method used in our screening studies is *in situ*-PHIP-NMR spectroscopy (PHIP = *Para-Hydrogen Induced Polarization*), which allows one to identify the very position where the parahydrogen is incorporated into the substrate. For every possible case, a specific pattern of absorption and emission signals results for the NMR spectra of the product.⁴ This may

include both the hydrogenation product and the substrate molecule; i.e., the latter only, if the reaction is (at least in part) reversible. Due to the fact that the characteristic PHIP spectrum is only observed if the parahydrogen is transferred pairwise by the catalyst without losing the pair correlation between the two former parahydrogen protons, one can identify very useful details about the mechanism by which the catalyst enables the hydrogen to exchange. In addition, one can determine the effects of the solvent, pressure, temperature, additives, etc.

2. Experimental Section

We report here on the investigation of the properties of the ruthenium system $\text{H}_2\text{Ru}(\text{PPh}_3)_4$, which is commercially available and has been identified and described earlier as a suitable homogeneous catalyst for hydrogenation and hydroformylation.⁵ We have found that this compound catalyzes the hydrogenation of styrene in benzene at room temperature, for example at a pressure of 3 bar of hydrogen, via the catalytically active species $\text{H}_2\text{Ru}(\text{PPh}_3)_3$, which hydrogenates via a pairwise transfer of hydrogen.⁶ The intermediate has been proposed to be $\text{H}_4\text{Ru}(\text{PPh}_3)_3$.⁷ In our experiments the H_2 -pressure was limited to 3 bar because we used simple glass NMR-tubes equipped with a gas-tight screw cap and a septum. The septum allows one to add well-defined and even minute amounts of gases and liquids to the reaction mixtures.

In the presence of CO, a change in the catalytic behavior has been observed, which is accompanied by exchange of the olefinic protons of styrene supplied as the substrate in benzene. In the presence of parahydrogen we observe the strong polarization signals of the hydrogenation product, namely of ethylbenzene ($\delta = 1.22/2.62$ ppm). This means that the two hydrogen atoms, which are catalytically added to styrene, originate from the same parahydrogen molecule and maintain their pair correlation throughout the reaction. Furthermore, polarization signals are also observed in the starting material styrene, making it obvious that the addition of the hydrogen

is reversible. ($^1\text{H-NMR}$ data of styrene in benzene- d_6 at 200 MHz: $\delta = 5.20$ [dd, $^2\text{J}(\text{H}^2\text{H}^3) = 1.2$ Hz, $^3\text{J}(\text{H}^2\text{H}^1) = 10.8$ Hz], $\delta = 5.72$ [dd, $^2\text{J}(\text{H}^3\text{H}^2) = 1.2$ Hz, $^3\text{J}(\text{H}^3\text{H}^1) = 17.6$ Hz], $\delta = 6.70$ [dd, $^3\text{J}(\text{H}^1\text{H}^2) = 10.8$ Hz, $^3\text{J}(\text{H}^1\text{H}^3) = 17.6$ Hz].) As shown in previous publications, the polarization in the starting material proves the reversibility and pairwise exchange of the protons of styrene. This was demonstrated for a Rh(I) and a Pd(0) catalyst as well, and a plausible mechanism for this reaction has been proposed.^{8,9}

To investigate the effect of CO on the reaction and its kinetics more precisely, a series of new experiments has been conducted using styrene- d_8 , thereby eliminating signals from the substrate. In this way, the polarization and thermal signals of styrene do not overlap. The addition of various amounts of CO to the atmosphere within the pressure tube has the following effect on the catalytic behavior of the ruthenium catalyst (Fig. 1): Solutions with a mole fraction of CO of 0, 50, 500, and 5000 mol%, respectively, have been investigated using PHIP NMR spectroscopy. Due to the small volume in the NMR tube and safety limitations, a further increase of the CO mole fraction is not feasible or is at least not advisable under these conditions. Already the addition of 50 mol % of CO (based on the mole fraction of the dissolved catalyst) leads to strong polarization signals at the chemical shift of the olefinic protons of styrene ($\delta = 5.20$ and 5.72 ppm). The exchange of hydrogen between styrene- d_8 and parahydrogen is accelerated by the addition of CO to the solution, whilst the rate of hydrogenation is reduced. This is confirmed by the "thermal", i.e., regular NMR spectrum of the products of the reaction (Fig. 2): In the absence of CO, the spectrum shows mainly the hydrogenation product ethylbenzene and only a small amount of the exchange product, both displaying polarization. In the presence of CO, however, the exchange product becomes strongly dominant over the hydrogenation product. In case of hydrogenations, in which large amounts of CO are present (Fig. 2b), no reduced product (ethylbenzene) was observed. Since neither an enlargement of this specific aliphatic region nor an increased number of scans showed product resonances, we conclude that no reduced product has been

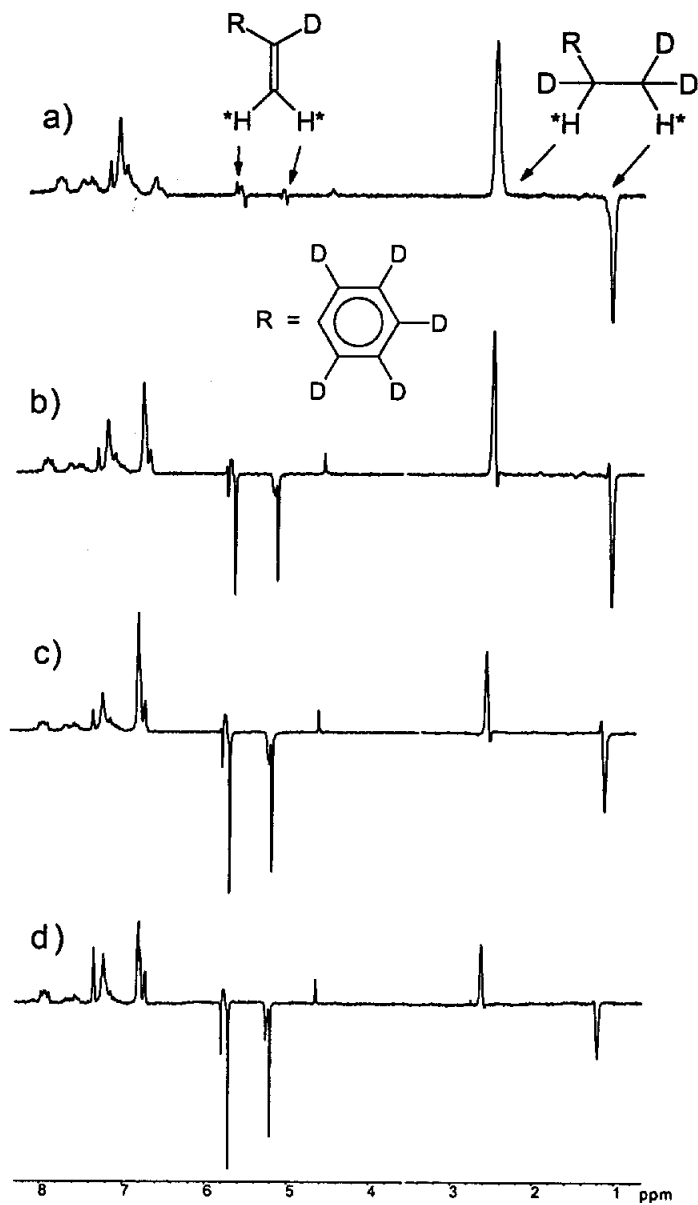


Figure 1. ^1H *in situ* PHIP-NMR spectra during the hydrogenation of styrene- d_8 using $\text{H}_2\text{Ru}(\text{PPh}_3)_4$ in benzene- d_6 , showing the changing polarization patterns as a consequence of added CO: a) without CO, b) 50 mol % CO, c) 500 mol % CO, d) 5000 mol % CO.

formed. Additionally, we conclude from Fig. 1 that the broadening of the resonances because of H/D - coupling is a minor effect and can be neglected.

The addition of CO not only increases the rate of hydrogen isotope exchange, but it also enhances the selectivity of this reaction. Because enhanced catalyst selectivity coincides with diminished activity, the signal intensities of the hydrogen isotope exchange product in Fig. 2b (presence of CO, $\delta = 5.22 - 5.76$ ppm) are much smaller than the intensities of the same signals in absence of CO (Fig. 2a) even if the same reaction conditions apply.

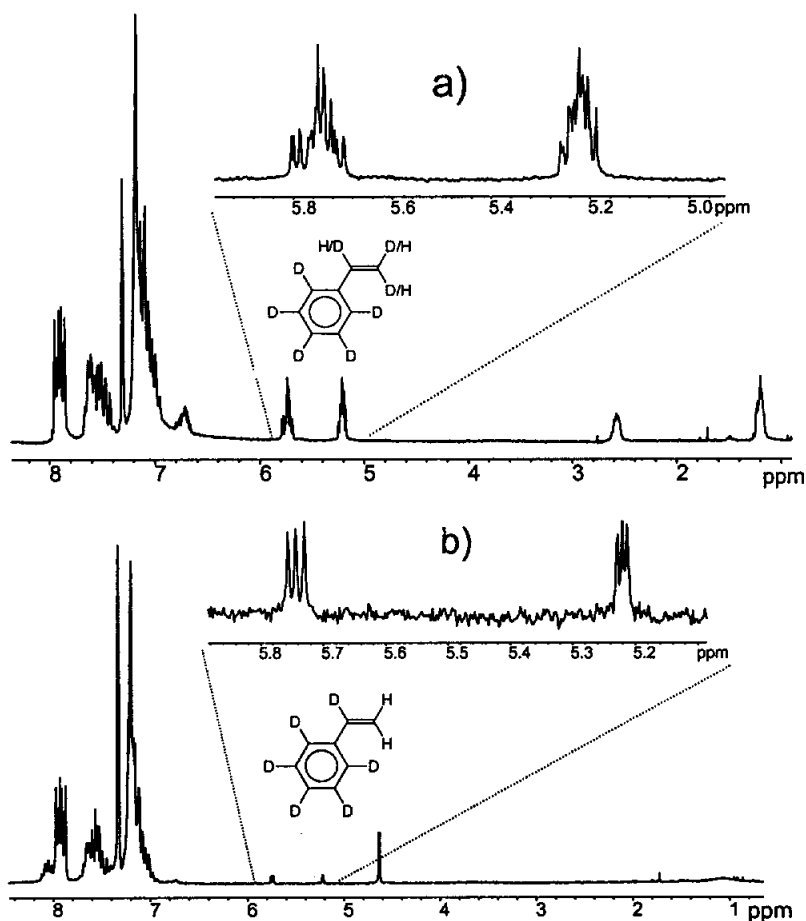


Figure 2. ¹H NMR spectra of the products formed in the hydrogenation of styrene-d₈ with H₂Ru(PPh₃)₄ in benzene-d₆: a) no CO added, b) 5000 mol % CO added.

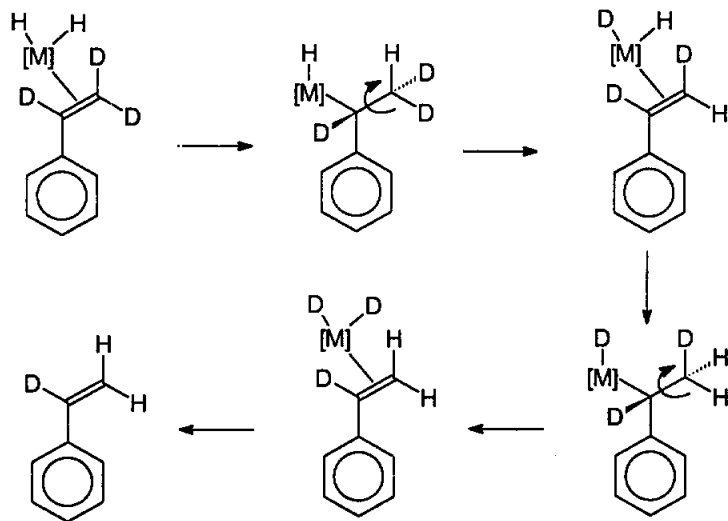
Without CO, a random exchange (at a lower rate than the hydrogenation) of the olefinic deuterium of the styrene- d_8 against hydrogen takes place. Due to the deuterated styrene- d_8 , the specific exchange of deuterium against protons stemming from parahydrogen is easily visible both in the "thermal" and the polarization spectra, because the ^1H -resonances of all of the three olefinic hydrogen atoms of styrene can easily be distinguished. Accordingly, the NMR spectrum obtained in the presence of CO exclusively shows a selective exchange of the geminal protons in the vinyl part of styrene. Both geminal styrene protons appear as triplets due to the H/D-coupling (deuterium, $I = 1$) with the methine deuteron; therefore, no significant exchange of the latter seems to occur, because this would also destroy the simple triplet appearance of the geminal alkene protons.

To clarify the interpretation of the spectra shown in Figs. 2a and 2b we point out that the signals visible in the aromatic region originate from the triphenylphosphine ligands of the homogeneous ruthenium catalyst, $\text{H}_2\text{Ru}(\text{PPh}_3)_4$, used in these reactions. In contrast to the perdeuterated substrate (i.e., styrene- d_8) the ligands of the catalyst have not been perdeuterated; therefore strong resonances appear in the region between $\delta = 6.7$ and 8.0 ppm including a signal from residual protons of benzene- d_6 ($\delta = 7.35$ ppm). All resonances of interest appear in the olefinic (styrene) and aliphatic region (ethylbenzene) of the spectra. We do not expect changes in the aromatic region because reactions in which aromatic protons are exchanged require more drastic reaction conditions (e.g., higher reaction temperatures). Hence, we did not need to use perdeuteration for the compounds that are only showing resonances in the aromatic region.

3. Conclusions

The appearance of polarization signals illustrates the simultaneous hydrogen isotope exchange of two deuterons against parahydrogen, i.e., while maintaining the pair correlation of the two former parahydrogen atoms. A mechanism proposed for this type of hydrogen isotope exchange reaction is

shown in Scheme 1.⁹ As the hydrogenation activity of the catalyst decreases in the presence of CO, both the rate of the exchange reaction and its selectivity increase and lead to exchange of the geminal deuterons in the alkene group of styrene. It is to be noted that no evidence for any hydroformylation has been found in our investigation under these conditions, neither by PHIP-NMR spectroscopy nor by any trace of the expected hydroformylation products in the final spectrum. This may be due to the fact that hydroformylation would require a high pressure of CO when using the described catalyst.⁵ Even though we cannot give a detailed quantitative analysis of the relation between the concentration of CO and its impact on reactivity and selectivity of the hydrogen isotope exchange yet, we conclude that the effect is non-linear. It is obvious that the difference in reactivity between 50 and 500 mol% CO is much more pronounced than that between 500 and 5000 mol %. All samples have been investigated applying the same conditions, especially the same pressure, temperature, concentration of the catalyst and substrate, and the same reaction time. Therefore, the variation of the signal intensities appear to be related with various amounts of CO in the tube and does not appear to be due to a variation in the conditions applied.



Scheme 1. Proposed mechanism for the metal-catalyzed exchange of the geminal protons of the alkene group of styrene.⁹

We are also convinced that the reaction is strictly catalytic because the effect of CO on the reaction can be reproduced many times, even when there is already a fair amount of the final product present - namely both ethylbenzene and already proton-exchanged styrene; therefore, at that point, there should hardly be any catalyst molecules left unused. Accordingly, CO does not seem to poison the catalyst.

The reaction outlined here provides a good method for introducing either tritium or deuterium into defined positions of alkenes, - here outlined for styrene only. Investigations are under way to extend the scope of this reaction to other positions and target molecules. Variation of the conditions may lead to other defined products using different catalysts, which can be screened using PHIP efficiently and accurately.

4. Acknowledgements

We gratefully acknowledge financial support from the Deutsche Forschungs-Gemeinschaft (DFG), the German Federal Ministry for Science and Technology (BMBF), the Forschungsverband Nordrhein-Westfalen, and the Fonds der Chemischen Industrie, Frankfurt (Main). We thank W. Keim and B. Driessen-Hoelscher, Institute of Technical Chemistry and Petrolchemistry, Technical University of Aachen, for stimulating discussions and suggestions.

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