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New Perspectives for Parahydrogen-Induced Polarization in Liquid Phase Heterogeneous Hydrogenation: An Aqueous Phase and ALTADENA Study

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Since parahydrogen-induced polarization (PHIP) phenomenon was described,[1] it has become one of the important tools for the investigation of the mechanisms and kinetics of homogeneous hydrogenation and hydroformylation reactions.[2] Polarization of nuclear spins provided by the utilization of parahydrogen in a catalytic hydrogenation reaction can be orders of magnitude higher than the thermal one. Therefore, owing to a significant signal enhancement in NMR spectra, it is possible to study fast reactions and to identify intermediates of a catalytic reaction even if their concentration in solution is low.[3] Homogeneous hydrogenation with parahydrogen was also successfully utilized for signal enhancement in magnetic resonance imaging (MRI).[4] However, the use of homogeneous catalysts and organic solvents in such experiments is a severe restriction to a much broader scope of PHIP applications in MRI. Clearly, for biomedical MRI the use of aqueous solutions is required. Up to now, several water soluble compounds were hydrogenated with parahydrogen to produce aqueous solutions of ^{13}C hyperpolarized contrast agents.[5] In all cases, however, homogeneous hydrogenation reactions were utilized. For in vivo MRI studies, transition metal complexes used as hydrogenation catalysts need to be removed from solution before the hyperpolarized agent is administered. Thus, a quick and facile removal of a hydrogenation catalyst from the polarized fluid would be essential for a successful application of PHIP in MRI experiments performed in vivo.

Obviously, heterogeneous catalysts are much easier to separate from a reaction mixture than homogeneous ones. Therefore, the use of heterogeneous catalysts in hydrogenation reactions could be an alternative route to produce catalyst-free hyperpolarized fluids. Besides, industrial catalytic processes are predominantly heterogeneous, and the studies of the nature of active sites and of the mechanisms of heterogeneous catalytic reactions represent an extremely important area of research that could benefit from the utilization of PHIP effects. Recently, it was shown that it is indeed possible to observe PHIP effects in heterogeneous hydrogenation reactions catalyzed by transition metal complexes immobilized on solid supports.[6] The PHIP effects were demonstrated for heterogeneous hydrogenation reactions carried out in both liquid and gas phases. The resulting hyperpolarized fluids were successfully utilized for gas phase MRI studies.[7,8] However, leaching of immobilized metal complexes from the solid support into solution and aging of the immobilized catalysts represent serious problems that complicate their use in aqueous phase heterogeneous hydrogenation reactions.

A recent observation of PHIP effects in heterogeneous gas-phase hydrogenation reactions catalyzed by supported metal catalysts[9,10] opens up new horizons for this field of research. Later it was confirmed that supported metal catalysts are able to produce PHIP effects in liquid phase hydrogenations as well.[11] In order to turn these observations into useful experimental protocols for MRI studies, it is essential to make further steps in the exploration of PHIP in heterogeneous hydrogenation reactions catalyzed by supported metal catalysts. Moreover, contrast agents typically used for clinical applications of MRI are water soluble.[12] Therefore, the production of water soluble polarized contrast agents is essential for extending PHIP MRI applications to potential in vivo studies.

With these goals in mind, we herein compare the PHIP effects observed for two catalysts comprising rhodium particles supported on two different porous supports and for the first time report the use of supported metal catalysts for the observation of parahydrogen induced polarization in an aqueous phase heterogeneous hydrogenation and of strong ALTADENA[1c] effects for heterogeneous hydrogenation of liquids and gases dissolved in several organic solvents.

For the initial study of the activity of the two supported metal catalysts, both Rh/TiO_2 and Rh/AlO(OH) catalysts were used in a heterogeneous hydrogenation of propylene gas (see the Supporting Information). It was established that these catalysts are very active in the gas-phase hydrogenation of propylene into propane even at room temperature (RT); moreover, the PHIP effects were clearly observed when parahydrogen was used in the hydrogenation reaction. The results obtained in the hydrogenation of propylene with parahydrogen employing Rh/TiO_2 and Rh/AlO(OH) catalysts are shown in Figure S1 in the Supporting Information. The observation of PHIP in the heterogeneous hydrogenation of propylene verifies that the heterogeneous hydrogenation reaction involves a reaction route in which two hydrogen atoms of one hydrogen molecule are added to the same substrate molecule. At the same time, this pairwise hydrogenation reaction route is not a major one, and its contribution can be estimated as several percent.[9] Nevertheless, the observation of polarized multiplets in the NMR spectra demonstrates that successful utilization of supported metal catalysts for PHIP production is possible.

For the next set of experiments, Rh/TiO_2 and Rh/AlO(OH) catalysts are used in a heterogeneous hydrogenation of propylene gas dissolved in a liquid. Both catalysts hydrogenate propylene into propane when the hydrogenation reaction is car-

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ried out in toluene and Rh/TiO_2 catalyst hydrogenates propylene in acetone. Importantly, the PHIP effects are observed when the mixture of parahydrogen and propylene is bubbled through the NMR tube containing the solvent and the solid catalyst. The resulting spectra detected in the ALTADENA and PASADENA[1b] experiments for propylene hydrogenation over the Rh/AlO(OH) catalyst in perdeuterated toluene and for propylene hydrogenation over the Rh/TiO_2 catalyst in perdeuterated acetone are shown in Figures S2 and S3 in the Supporting Information, respectively. In agreement with the data reported in ref. [11], these results confirm that PASADENA polarization can be produced using supported metal catalysts for heterogeneous hydrogenation in a liquid phase when the reaction is carried out inside the NMR magnet. However, these results also demonstrate, for the first time, that supported metal catalysts can produce clear ALTADENA polarization patterns when the reactant mixture is bubbled through the sample outside the NMR magnet and the sample is then transferred to the high magnetic field for signal detection. Observation of ALTADENA polarized lines in the ^1H NMR spectra opens up the possibility to use supported metal catalysts for production of continuously flowing polarized liquids. Besides, conducting the hydrogenation reaction outside the NMR instrument provides more flexibility in the experiment design and the experimental conditions as compared to the hydrogenation performed within the restricted space of the NMR magnet and radiofrequency probe. For instance, much higher temperatures, pressures and larger reactor volumes can be used in ALTADENA experiments. Moreover, the polarization patterns provided by ALTADENA are convenient for subsequent MRI experiments since no or little modification of the standard MRI procedures is needed. In the case of ALTADENA experiments, one of the polarized inphase multiplets can be used for image acquisition directly,[8] while for PASADENA experiments the antiphase character of the polarization pattern of each multiplet initially results in zero net signal.

Once a polarized product molecule is produced, its polarization starts to decay due to nuclear spin relaxation processes. The relaxation is expected to be much faster for molecules residing in the pores of the supported catalysts than for molecules in a bulk fluid. Therefore, slow diffusional transport, especially in the liquid phase, can lead to significant polarization losses and even to a complete destruction of polarization while a polarized product molecule diffuses within a porous catalyst support. To verify that PHIP can be observed for slower diffusing molecules, styrene is chosen for further experiments as a higher molecular weight substrate. As a result, the two supported metal catalysts are found to hydrogenate styrene into ethylbenzene and to produce PHIP effects when parahydrogen is used in the reaction. The ^1H NMR spectra of PASADENA and ALTADENA experiments in which hydrogenation of styrene in perdeuterated acetone is performed with the Rh/TiO_2 catalyst are shown in Figure 1. The results demonstrate that observation of ALTADENA polarization patterns in liquid phase heterogeneous hydrogenation should be possible for a variety of substrates, and that the use of supported catalysts, without doubt, holds a potential for significantly broadening the range of PHIP applications.

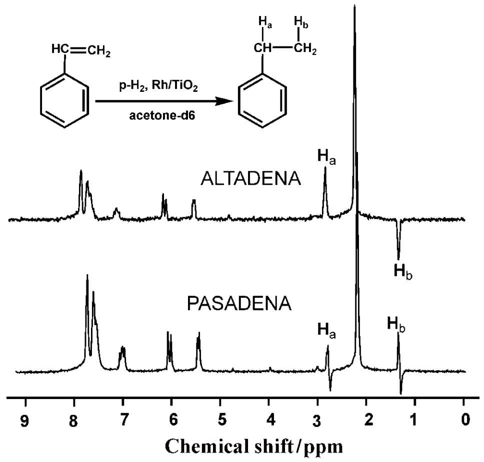

Figure 1. ^1H NMR spectra detected in the heterogeneous hydrogenation of styrene over Rh/TiO_2 supported metal catalyst in [D_6]acetone at RT in the case of PASADENA (bottom) and ALTADENA (top) experiments. The enhanced polarized lines of the CH_2 and the CH_3 groups of ethylbenzene are labeled H_a and H_b, respectively.

As it was mentioned above, the activity of the Rh/TiO_2 catalyst is higher than that of the Rh/AlO(OH) catalyst, which leads to an observation of PHIP effects for the Rh/TiO_2 catalyst even at RT in acetone. Therefore, the Rh/TiO_2 catalyst is further tested in the aqueous phase hydrogenation experiments. It is found that the Rh/TiO_2 catalyst hydrogenates acrylamide and allyl methyl ether when the heterogeneous hydrogenation reactions are carried out in D_2O at 353 K. Moreover, the clear PASADENA polarization patterns are observed when parahydrogen is used. The resulting spectrum detected during heterogeneous hydrogenation of acrylamide into propylamide in D_2O is shown in Figure 2.

Observation of the PHIP effect for aqueous phase hydrogenation confirms the preservation of the spin order of two H atoms as they are transferred from the same parahydrogen molecule to the same substrate molecule to produce the prod-

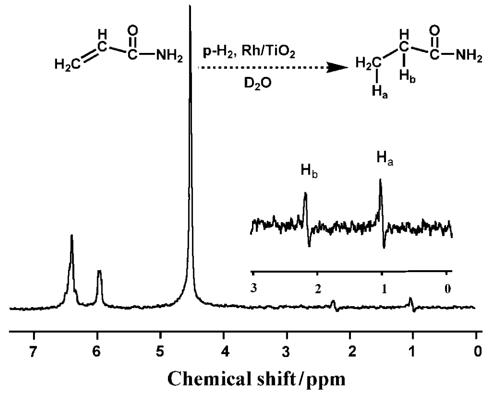

Figure 2. ^1H NMR spectrum detected in the heterogeneous hydrogenation of acrylamide over Rh/TiO_2 supported metal catalyst in D_2O at 353 K in the case of PASADENA experiment. The enhanced polarized lines of the CH_2 and the CH_3 groups of propylamide are labeled H_b and H_a, respectively.

uct. Hence, the route of the heterogeneous hydrogenation reaction by which hydrogenation proceeds in a pairwise manner is similar for hydrogenations in the aqueous phase, in organic liquids and in the gaseous phase and measurably contributes to the overall hydrogenation reaction.

In summary, observation of the clear ALTADENA polarization in the liquid phase during heterogeneous hydrogenation of dissolved gaseous and liquid substrates is reported for the first time for hydrogenation reactions catalyzed by supported metal catalysts. The ALTADENA experiment provides polarization patterns that can be easily combined with the standard MRI protocols with little or no modification. Besides, in contrast to a PASADENA experiment, the hydrogenation reaction in ALTADENA experiment is conducted outside the restricted space of a magnet of an NMR or MRI instrument. This provides more flexibility for optimizing the experimental conditions and is suitable for production of continuously flowing hyperpolarized fluids. The observation of PHIP effects in the aqueous phase hydrogenation of double bonds of amides and ethers catalyzed by supported metal catalysts is also reported. The first observation of PHIP produced with supported metal catalysts in an aqueous phase heterogeneous hydrogenation is very important for future medical MRI applications and for the verification of reaction mechanisms of aqueous phase heterogeneous catalytic reactions. Clearly, the systems reported above are not immediately suitable for in vivo MRI experiments, and further research is needed to optimize the procedures for PHIP production with higher signal enhancements. Nevertheless, the observation of the ALTADENA effect in the liquid phase hydrogenation and of the PASADENA effect in the aqueous phase hydrogenation represent a big step toward the hypersensitive in vivo MRI protocols where water soluble contrast agents along with an ease of recovery of a catalyst from the hyperpolarized liquid play a very important role. Importantly, the results reported here demonstrate that higher polarization levels can be achieved by systematically varying the nature of a solid support, the solvent, the substrate, and other experimental parameters and conditions.

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