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Authors: Gábor Papp, Henrietta Horváth, and Ferenc Joó

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A simple and efficient procedure for Rh(I)- and Ir(I)-complex catalyzed *para*-hydrogenation of alkynes and alkenes in aqueous media resulting in strong PHIP effects

Dr. Gábor Papp,*[a] Dr. Henrietta Horváth[b] and Prof. Dr. Ferenc Joó[a,b]

Abstract: Catalytic hydrogenations with *para*-H_2 may lead to strong *para*-hydrogen induced polarization (PHIP) and the hyperpolarized probe molecules may enable the application of the Magnetic Resonance Imaging (MRI) diagnostic modality for metabolism imaging. The use of water as a solvent for *para*-hydrogenation reactions is very challenging due to the fast exchange between the catalytically active metal hydrides and the water protons and also because of the low hydrogen solubility in water. Here we report that several water-soluble Rh(I)- and Ir(I)-complexes with N-heterocyclic carbene (NHC) and/or tertiary phosphine ligands efficiently catalyze the synthesis of hyperpolarized compounds by *para*-hydrogenation in aqueous media.

The use of ***p**ara*-**h**ydrogen **i**nduced **p**olarization (PHIP) was initiated by Bowers and Weitekamp in 1986.[1] In case the hydrogen gas consists of mostly the *para*-H_2 isomer, the polarization of hydrogen atoms in H_2 will be transferred to the corresponding carbon atom in the hydrogenation reaction by scalar coupling. Furthermore, the addition of the two spin isomeric H atoms should happen pairwise, i.e. the relative spin directions must be retained.[1,2] In other words, activation of *para*-H_2 must proceed on the homolytic pathway. PHIP leads to 10^4-10^5 times higher NMR intensities of the appropriate C-atom resonances in the ^{13}C-spectra and this sensitization gives a chance to detect substances, such as e.g. various intermediates in catalytic reactions even at picomol concentration level. Furthermore, this sensitivity makes possible the MRI[3] of live targets such as cells, laboratory animals or even human patients. An important parameter in such experiments is the lifetime of the hyperpolarized probe molecules, which generally spans the 1-5 minutes interval.

The water solubility of spin-labelled probe molecules is a very important feature for MRI and other medical diagnostic procedures. Despite this, only a few examples exist when the target molecules are prepared in aqueous media.

The hyperpolarized 1-^{13}C-phospholactate-d_2 was obtained in aqueous solution from the 1-^{13}C-phosphoenolpyruvate-d_2 by PHIP with a Rh(I)-catalyst,[4] $[Rh(I)(norbornadiene)(THP)_2]^+[BF_4]^-$ (THP = tris(hydroxymethyl)phosphine).[5] Cationic Rh(I)-phosphine complexes were applied as *para*-hydrogenation catalysts also in other reactions to induce PHIP in aqueous media.[6] Hyperpolarized succinic-acid[7] or pyruvate[8] which allow metabolic imaging were synthesized by *para*-hydrogenation of maleic anhydride or 2-propynyl-2-oxopropanoate in organic solutions with a $[Rh(cod)(dppb)][BF_4]$ catalyst (cod = 1,5-cyclooctadiene, dppb = 1,4-bis(diphenylphosphino)butane), and the water-soluble hyperpolarized target molecules were obtained by post-hydrogenation modifications, such as hydrolysis. Very recently Münnemann and co-workers disclosed a procedure for preparation of hyperpolarized fumarate via PHIP by using $[Cp^*Ru(CH_3CN)_3]PF_6$ (Cp^* = pentamethylcyclopentadienyl) as a catalyst).[9]

As can be seen from this brief overview, the choice of hydrogenation catalysts suitable for PHIP applications in water is rather limited both by mechanistic requirements[1,2] and by solubility properties. Ionic Rh(I)[4] and Ru(II)[9] complexes may show sufficient water-solubility to be useful in aqueous hydrogenations. Conversely, heterogeneous catalysts, and water-insoluble or heterogenized metal complexes can be used for hydrogenation of water-soluble substrates only in biphasic (solid/liquid or liquid/liquid) systems generally characterized by low reaction rates.

Research into aqueous homogeneous organometallic catalysis has led to the development of a wide array of water-soluble hydrogenation catalysts.[10] Some of them were successfully applied for modification of biological membranes by catalytic hydrogenation both in model systems and in living cells, demonstrating also their sufficient biocompatibility.[10f,g] In this work, we show that several water-soluble catalysts can be used advantageously for *para*-hydrogenation of appropriate water-soluble substrates for the synthesis of important hyperpolarized probe molecules for MRI purposes in aqueous media. The use of PHIP allowed by such catalysts may usefully contribute to the MRI of living systems (from cells to higher organisms).

The catalysts for *para*-hydrogenation were prepared in situ, by reactions of *m*tppms (monosulfonated triphenylphosphine)[11] or *m*tppts (trisulfonated triphenylphosphine)[12] with $[\{RhCl(cod)\}_2]$, $[\{IrCl(cod)\}_2]$, [RhCl(cod)(NHC)], or [IrCl(cod)(NHC)][10e], where NHC = 1,3-dialkyl- or 1,3-diarylimidazole-2-ylidene (Figure 1). The aqueous solubility of these complexes is the result of the coordination of *m*tppms or *m*tppts. In addition, *cis,mer*-$[IrH_2Cl(mtppms)_3]$[13] was also used the first time as catalyst in PHIP studies in water.

[a] University of Debrecen
Department of Physical Chemistry
Debrecen, P.O.Box 400, H-4002 Hungary
E-mail: papp.gabor@science.unideb.hu
Homepage: https://fizkem.unideb.hu
[b] MTA-DE Redox and Homogeneous Catalytic Reaction Mechanisms Research Group
Debrecen, P.O.Box 400, H-4002 Hungary

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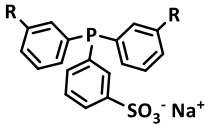
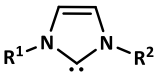


R = H: ***m*tppms**
R = SO_3Na: ***m*tppts**



R^1 = CH_3 R^2 = C_2H_5: **emim**
R^1 = CH_3 R^2 = C_4H_9: **bmim**
R^1, R^2 = 2,4,6-$(Me)_3C_6H_2$: **IMes**
R^1, R^2 = 2,6-$(i\text{Pr})_2C_6H_3$: **IPr**

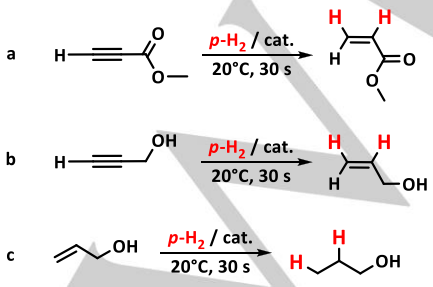
Figure 1. Phosphine and N-heterocyclic carbene ligands used in this study

In this study, we investigated the *para*-hydrogenation of methyl propynoate (one of the most widely used substrates for PHIP studies), propargyl alcohol, and allyl alcohol (Scheme 1). This is the first report on the use of mixed ligand N-heterocyclic carbene/tertiary phosphine Rh(I)- and Ir(I) complexes for *para*-hydrogenation in purely aqueous solutions. In fact, the Ir(I)-N-heterocyclic carbene and carbene/phosphine hydride complexes represent the major type of catalysts in studies of SABRE (Signal Amplification By Reversible Exchange). In that case, the polarization transfer from *para*-hydrogen to the substrate molecule takes place via ligand exchange in the coordination sphere around the transition metal centre, however, no hydrogenation is involved in the process.[14]

Hydrogenations with *para*-H_2 were performed in 5 mm NMR tubes. The reaction protocol consisted of a) pre-hydrogenation of the catalyst solution; b) freezing the sample in liquid N_2; c) addition of the substrate and filling the tube with *para*-H_2; d) thawing the sample and performing the *para*-hydrogenation, e) ^{1}H-NMR detection of the products. The hyperpolarized products were detected by ^{1}H-NMR spectroscopy with 45° flip angle and OPSY[15] measurements.

In general, *para*-hydrogenations were studied in water:methanol = 9:1 mixtures (although water alone could also be used; see Experimental). The active hydrogenation catalysts obtained in reactions of the methanol-soluble *m*tppms with [{RhCl(cod)}$_2$] or [{IrCl(cod)}$_2$] which were applied also in MeOH.

As a result of *para*-hydrogen addition to methyl propynoate, the product methyl acrylate showed the special shape of polarized ^{1}H-NMR signals confirming hyperpolarization (Figure 2). With both catalysts, about 3 min lifetime of polarization was detected.



Scheme 1. Catalytic *para*-hydrogenation of methyl propynoate in MeOH (**a**) and that of propargyl alcohol and allyl alcohol in aqueous media (**b,c**). (For the actual catalysts and solvents see Table 1.)

The catalysts, listed in entries 1-4 in Table 1, proved suitable for *para*-hydrogenation in aqueous media of both propargyl alcohol (Scheme1-**b**) and allyl alcohol (Scheme1-**c**). Similarly, propargyl alcohol was efficiently *para*-hydrogenated with the mixed ligand NHC/sulfonated triphenylphosphine Rh(I)- and Ir(I)-complex catalysts – as shown by the polarised signals detected by normal ^{1}H-NMR spectroscopy with 45° flip angle and ^{1}H-NMR-OPSY[20] measurements (Table 1, entries 5-12). By performing the experiments in aqueous media the lifetime of polarized signals was found to be in the range of 1-3 minutes.

Table 1. PHIP-activities of in situ formed Rh(I)- and Ir(I)-complexes in *para*-hydrogenation reactions of propargyl alcohol and allyl alcohol in aqueous media (**+**: polarized signals detected; **–**: no polarized signals). The corresponding ^{1}H-NMR spectra are shown in Figure 2 and in the Supporting Information.

		propargyl alcohol[a]	allyl alcohol[a]
1	[{RhCl(cod)}$_2$] + 6 *m*tppms[b]	**+**	**+**
2	[{IrCl(cod)}$_2$] + 6 *m*tppms[b]	**+**	**+**
3	[{RhCl(cod)}$_2$] + 6 *m*tppts	**+**	**+**
4	[{IrCl(cod)}$_2$] + 6 *m*tppts	**+**	**+**
5	[IrCl(cod)(bmim)] + 3 *m*tppms	**+**	**–**
6	[IrCl(cod)(bmim)] + 3 *m*tppts	**+**	**–**
7	[IrCl(cod)(emim)] + 3 *m*tppms	**+**	**–**
8	[IrCl(cod)(emim)] + 3 *m*tppts	**+**	**–**
9	[RhCl(cod)(IMes)] + 3 *m*tppms	**+**	**+**
10	[RhCl(cod)(IMes)] + 3 *m*tppts	**+**	**+**
11	[RhCl(cod)(IPr)] + 3 *m*tppms	**+**	**–**
12	[RhCl(cod)(IPr)] + 3 *m*tppts	**+**	**+**

a] in D_2O:CD_3OD = 9:1; [b] also in CD_3OD

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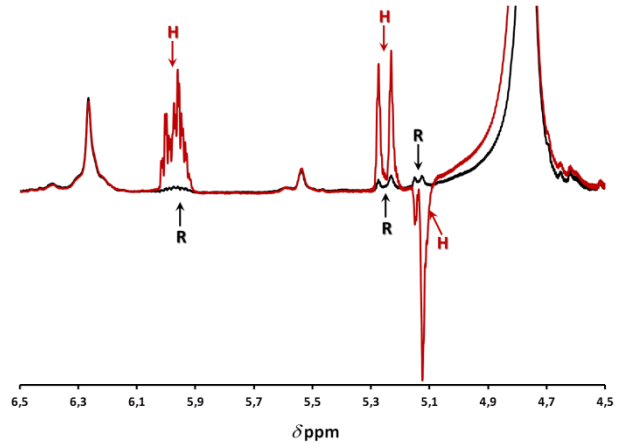

Figure 2. Hyperpolarized (**H**, red) and relaxed (**R**, black) ^{1}H-NMR spectra of *para*-hydrogenated propargyl alcohol. [RhCl(cod)(IPr)] = 25 mM; [*m*tppms] = 75 mM; [propargyl alcohol] = 200 mM; $P_{para\text{-}H2}$ = 1.5-1.6 bar (*T*=77K) (~ 6 bar, *T*=293K); *V*(solvent) = 0.4 mL. (Table 1. entry 13)

During prehydrogenation, the 1,5-cyclooctadiene ligand in the Rh(I)- or Ir(I)- catalyst precursor is transformed to free cyclooctane, a known biomembrane fluidizing agent. Recently we have synthesized the highly water-soluble, *cod-free* Ir(I)-*m*tppms hydrogenation catalyst, *cis,mer*-[IrH$_2$Cl(*m*tppms)$_3$],[13] soluble in MeOH. As demonstrated by the spectra in Figure 3, methyl propynoate was efficiently *para*-hydrogenated in CD_3OD by this catalyst which led to the expected high intensity inverse ^{1}H-NMR resonances. The polarized signals were detected for more than five minutes after the polarization occurred.

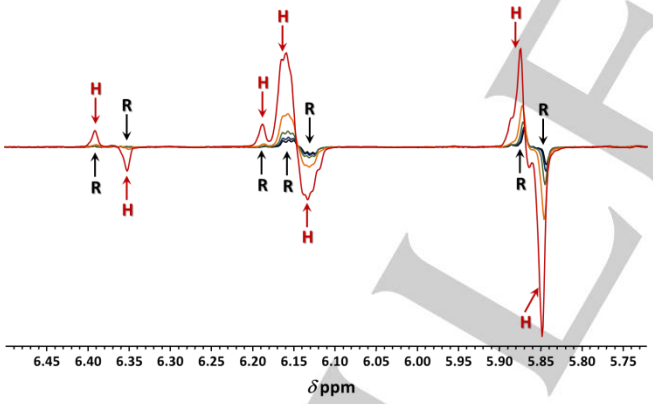

Figure 3. Hyperpolarized ^{1}H-NMR signals of *para*-hydrogenated methyl propynoate. [*cis,mer*-[IrH$_2$Cl(*m*tppms)$_3$]] = 25 mM; [methyl propynoate] = 200 mM; $P_{para\text{-}H2}$ = 1.6 bar (*T*=77K), (~6 bar, *T*=293K); *V*(solvent) = 0.4 mL, (**H** = hyperpolarized, **R** = relaxed).

The high catalytic activity of *cis,mer*-[IrH$_2$Cl(*m*tppms)$_3$] allows *para*-hydrogenation reactions not only in alcoholic solutions but also in water. For the hydrogenation of propargyl alcohol, the polarized signals and the changes in their intensities in time are shown in Figure 4.

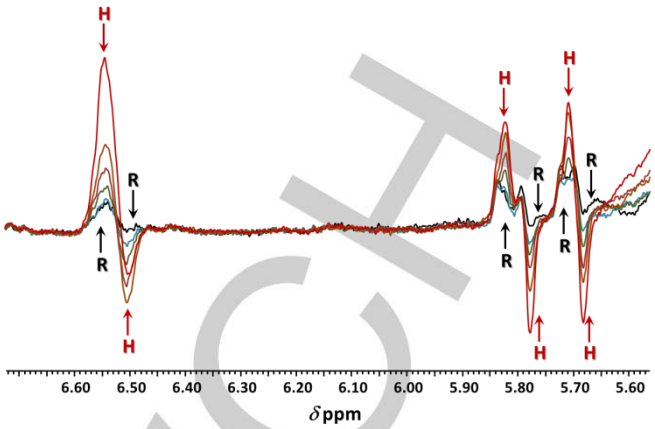

Figure 4. *Para*-hydrogenation of propargyl alcohol in aqueous media (water:methanol = 9:1). [*cis,mer*-[IrH$_2$Cl(*m*tppms)$_3$]] = 25 mM; [propargyl alcohol] = 200 mM; $P_{para\text{-}H2}$ = 1.6 bar (*T*=77K), (~6 bar, *T*=293K); *V*(solvent) = 0.4 mL, (**H** = hyperpolarized, **R** = relaxed).

The lifetime of polarisation is about 1 min, shorter than in pure methanol (5 min), yet it is clearly detectable with 45 degree flip angle NMR-measurements (Figure 4).

In conclusion, it is demonstrated here, that with the use of catalysts hitherto not applied for *para*-hydrogenations in aqueous solutions, such as Rh(I)- and Ir(I)- mixed ligand sulfonated phosphine/N-heterocyclic carbene complexes and *cis,mer*-[IrH$_2$Cl(*m*tppms)$_3$], efficient *para*-hydrogenation of alkynoic and alkenoic substrates could be realized in aqueous media. In water as a solvent, the hyperpolarized ^{1}H-NMR signals persisted for approximately 1-3 minutes, while up to 5 minutes in methanol. These systems allow synthesis of hyperpolarized molecules which in turn can be applied as contrast enhancement agents for MRI in aqueous media.

Experimental Section

0.400 mL of the catalyst solution (25 mM, P/Rh or P/Ir = 3) was prepared in a Schlenk-tube under an argon atmosphere and the catalytically active species was obtained by bubbling of H_2 (“normal” hydrogen) in the pre-activation step. Next, the solution was placed into a 5 mm NMR tube equipped with Quick-Pressure valve. The substrate (200 mM) was added and the tube was pressurized with 1.5-1.6 bar of *para*-H_2, while keeping it in liquid nitrogen to achieve a higher *para*-hydrogen partial pressure and to freeze any hydrogenation reaction. The reaction mixture was let to thaw at room temperature and then vigorously shaken for about 30 seconds. (According to the NMR spectra, this simple procedure resulted in 40-50% conversion of the starting unsaturated alcohols.) Immediately, the sample was placed into the NMR spectrometer and the hyperpolarized ^{1}H-NMR signals were recorded by 45° flip angle or OPSY measurements.[15] In general, the aqueous solvents contained 10% methanol, although the hydrogenations could be run with water alone. Nevertheless, in the presence of methanol, thawing of the reaction mixtures frozen at 77 K takes place faster and close to perfect shimming of

the NMR equipment also requires less time – both are important aspects with probe lifetimes of 1-3 minutes.

Acknowledgements

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Keywords: *para*-hydrogenation • PHIP • aqueous media • transition metals • homogeneous catalysis

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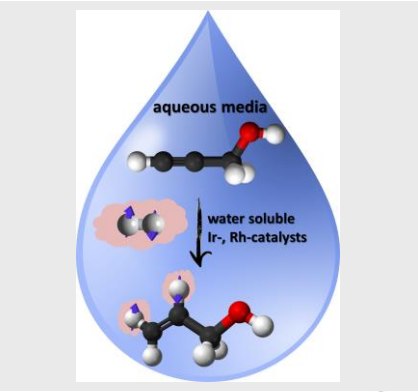
Rh(I)- and Ir(I)- mixed ligand sulfonated phosphine/N-heterocyclic carbene complexes, as well as *cis,mer*-[IrH_2Cl(*m*tppms)$_3$], are reported as efficient catalysts for *para*-hydrogenation of unsaturated substrates in aqueous media. A simple procedure is reported for obtaining hyperpolarized probe compounds which may be useful in MR metabolism imaging.



***Para*-Hydrogenation**

Gábor Papp, Henrietta Horváth, Ferenc Joó*

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A simple and efficient procedure for Rh(I)- and Ir(I)-complex catalyzed *para*-hydrogenation of alkynes and alkenes in aqueous media resulting in strong PHIP effects

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