Examination of hyperpolarization in aqueous media with *para*-hydrogen

Project closing report – Final report

In the last year of the project, the studies of *para*-hydrogenation reactions in aqueous media were further studied – in accord with the original research plan. My earlier results proved that several water soluble Rh- and Ir-NHC-phosphine complexes were active catalysts for *para*-hydrogenation.

Propargyl alcohol (this alkyne was used as a water soluble model for biogically relevant compounds) was para-hydrogenated by Rh-hydroxo-NHC complexes containing bulky N-heterocyclic carbenes (iMes and iPr) and the polarized signals were detected by different NMR-methods (namely the „**O**nly **P**arahaydrogen **S**pectroscop**Y**" and the generally used „45° flip angle measurement" - 1 scans).

With this substrate, the highest polarization lifetime was 10 minutes, i.e. the polarized signals were detected even after 10 minutes following the para-hydrogenation – this results was really promising for the further applications because the „normal" lifetime of polarization is 60-120 seconds.

Propargyl and allyl alcohols were also tested as model substrates in *para*-hydrogenation reactions in aqueous media with different Ir-NHC-sulfonated phosphine complexes (NHC = emim = 1-ethyl-3-methylimidazol-2-ylidene and the sulfonated phosphines were the mono- and tri-sulfonated triphenylphosphines). The polarized ^{1}H-NMR signals were also detected by the above mentioned NMR-methods (*Figure 1.*). Polarization lifetime (approximately 3 minutes) was among the longest similar lifetimes available in the literature.

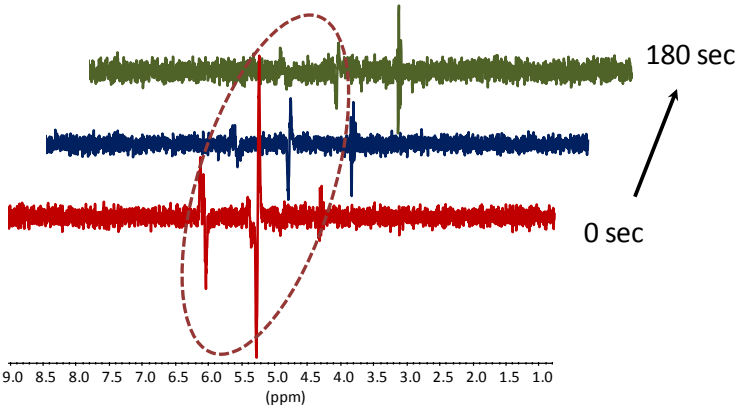

Figure 1.: ^{1}H-hyperpolarized NMR-signals in *para*-hydrogenation reaction of propargyl alcohol with [IrCl(cod)(emim)] + *m*tppms catalyst system - **OPSY** measurement

In accord with the research plan, various water soluble unsaturated substrates (itaconic acid, maleic acid, crotonic acid, pyruvate, etc.) were applied as model substrates in (*para*)-hydrogenation reactions with different Ir-complex catalysts in aqueous media. The reaction kinetics of these hydrogenation reactions were studied with {[Ir(emim)(cod)(L)] + L} (L = *m*tppms and/or *m*tppts). The effect of substrate/catalyst ratio, temperature, hydrogen pressure, phosphine excess, pH were measured and it was concluded that these catalytic systems are appropriate for *para*-hydrogenation test reactions. For example, the temperature and time dependence of pyruvate hydrogenation are shown in *Figure 2.*

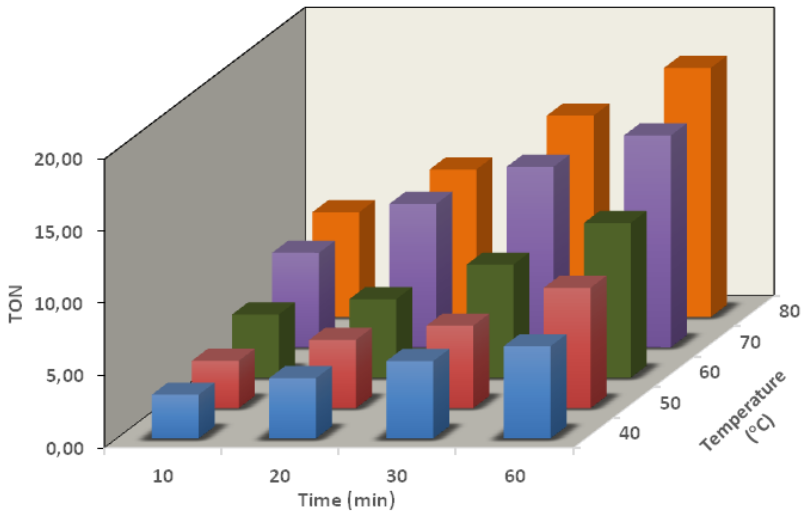

Figure 2.: **T**urn **O**ver **N**umbers in pyruvate hydrogenation as functions of reaction time and temperature

In accord with the main aim of the planned research, *para*-hydrogenations were studied in aqueous media, consequently various water-soluble Ir-complexes were applied as catalysts. We tried to prepare an active Ir-phosphine catalyst without a cod-ligand - this is most important for the possible further biological applications because during hydrogenation the cyclooctadiene gives rise to cyclooctane which is toxic to living organisms. The *cis,mer*-dihydride, $[IrH_2Cl(m\text{tppms})_3]$ (*m*tppms = monosulfonated triphenylphosphine) was prepared (and fully characterized by several analytical methods: IR, ESI-MS, elemental analysis, NMR, etc.) in a simple reaction between hydrated Ir(III)-chloride and *m*tppms.

The new Ir-*m*tppms-dihydride (*cis,mer*-$[IrH_2Cl(m\text{tppms})_3]$) was studied in *para*-hydrogenation reactions, as well. Methyl-propiolate was tested in *para*-hydrogenation reaction in methanol with this Ir-complex (it is quite soluble in MeOH) under different circumstances. The polarized ^{1}H-NMR signals appeared in the corresponding spectra (*Figure 3.* ***A***) and the specific shape of these signals were observed for more than 5 minutes (meaning that the lifetime of polarization was quite high). Encouraged by the high activity of Ir-dihydride complex in *para*-hydrogenation reaction in methanol, we also studied para hydrogenation reactions in aqueous media.

Methyl propiolate is only fairly soluble in water, so in aqueous media we studied para-hydrogenation of water soluble substrates, such as propargyl and allyl alcohols catalyzed by *cis,mer*-$[IrH_2Cl(m\text{tppms})_3]$ complex (*Figure 3.* ***B***). However, the observed polarization lifetime (~1 minutes) was shorter than in MeOH. In summary, the polarized signals were detected in the NMR spectra; further advantages of this reaction are in that the applied Ir-complex there are no toxic ligands, furthermore, the measurements were done in plain water.

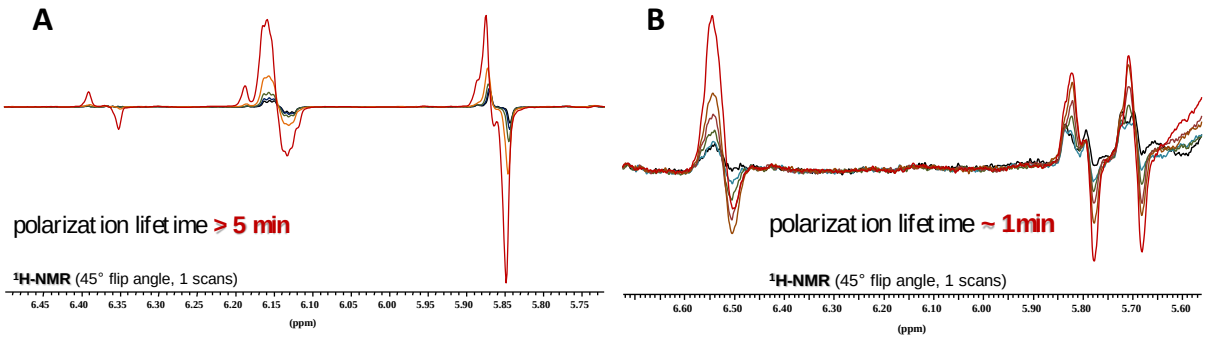

Figure 3.: The polarized signals in *para*-hydrogenation reaction with cis,mer-[IrH_2Cl(*m*tppms)$_3$] catalyst in methyl propiolate (**A**) (in CD_3OD) and propargyl alcohol (**B**) (in aqueous media)

Propargyl and allyl alcohols were also tested as a model substrate molecules in *para*-hydrogenation reactions in aqueous media with tha above Ir-complex catalysts and the polarization transfer was enhanced by field cycling. The special shape ^{1}H-NMR signals were detected by the "normal" 45°flip angle NMR-method and the **OPSY** measurements, as well. The intensity of these signals are 1.5-2 times higher than without field cycling and the polarization lifetime (approximately 2-3 minutes) was quite good but not superior to those observed by normal *para*-hydrogenation methods. The hyperpolarized ^{13}C-NMR signals did not appear in these spectra (not surprisingly, since we did not use ^{13}C-labelled substrates).

The *para*-hydrogenation of bicarbonate was studied with [{$RuCl_2$(*m*tppms)$_2$}$_2$] and [Ir(emim)(cod)(*m*tppts)] complex catalysts under differrent circumstances (excess of different phosphines, temperature, substrate ratio, *para*-hydrogen pressure, field cycling, etc.). The hyperpolarized ^{13}C-signal of formate wasn't detected but small amounts of formate were determined in these systems by normal NMR spectroscopy. It means that the mechanism of hydrogen activation is not suitable for *para*-hydrogenation. On the other hand the hyperpolarized free bicarbonate signal was not detected, either, probably because the exchange between the coordinated and free HCO_3^- is too slow. In addition, the **SABRE** (**S**ignal **A**mplification **B**y **R**eversible **E**xchange) effect was not observed in these systems, either, by field cycling techniques.

cis,mer-[IrH_2Cl(*m*tppms)$_3$] was an active catalyst in formic acid decomposition to hydrogen and carbon dioxide and in the back reaction (CO_2 to HCOOH), too. Formic acid is one of the most promising hydrogen storage material. The safe chemical storage of hydrogen in aqueous media is one of our other main research area.

cis,mer-[IrH_2Cl(*m*tppms)$_3$] was tested in homogeneous formic acid decomposition under different circumstances. The virtual activation energy was determined (79.6 kJ/mol) from the temperature dependence of reaction rate. Variation of the pH of the reaction mixture in the 2.0-8.5 range led to a sharp maximum of the rate at pH=3.75. Catalysis of formic acid dehydrogenation by this Ir-dihydride was also studied in a 100 mL Parr-reactor by following the resulting increase in pressure, the reaction proceeded with a TOF = 298 000 h^{-1} (it is the third most active catalyst known in this reaction) and the final total pressure was 71 bar. The stability of this catalyst are demonstrated in five subsequent cycles.

In a parallel research we studied a reversible hydrogen storage reaction system, based on hydrogenation of aqueous cesium bicarbonate and dehydrogenation of cesium formate homogeneously catalyzed with the water-soluble [Ir(cod)(emim)(*m*tppms)] in a flow reactor (H-Cube^{TM}). Fast switches of the reactor temperature between high (e.g. 100 °C) and low (e.g. 25 °C)

values allow precise and dynamic adjustment of the H_2 generation rate to application demand. Furthermore, depending on the relative volume of storage solution and the flow reactor, only a fraction of the reaction mixture has to be heated avoiding undesired H_2 evolution. This work also demonstrates the practical feasibility of using homogeneous catalysis for hydrogen generation in flow systems.

In a parallel project we proved that the bicarbonate acts as promoter in hydrogenation of cinnamaldehyde in aqueous systems with [{$RuCl_2$(*m*tppms)$_2$}$_2$] + *m*tppms catalyst. The bicarbonate assisted catalysis was demonstrated by reaction kinetic measurements and the catalytically active species were determined by multinuclear NMR methods. We suggested a complete catalytic reaction mechanism cycle.

We started a collaboration with András Guttman's group (Horváth Csaba Laboratory of Bioseparation Sciences, University of Debrecen, Hungary) and we tested the catalytic activity of the *cis,mer*-[IrH_2Cl(*m*tppms)$_3$] and the [{$RuCl_2$(*m*tppms)$_2$}$_2$] complexes in a most frequently used high-resolution glycan analysis method. We described a novel procedure for labeling N-glycans by fluorogenic primary amines via reductive amination, based on transfer hydrogenation from formic acid catalyzed by these water-soluble phosphine complexes. Similar labeling efficiencies were achieved with use of these catalysts to those observed with the traditionally used reducing agent $NaBH_3CN$. This procedure avoids the release of acutely toxic hydrogen cyanide, therefore, it is more environmentally friendly and eliminates the associated health risks.

Conclusion

The catalytic activities of several Ir-NHC-phosphine complexes were characterized in hydrogenation of unsaturated carboxylic acids. It was established that their catalytic properties allow their use in catalysis of *para*-hydrogenation reactions, too. A simple and effective methodology was developed for the application of Rh(I)- and Ir(I)-NHC/phosphine complex catalysts in *para*-hydrogenations in aqueous media – propargyl and allyl alcohols were used as model substrates. It was established that in these system application of decreased magnetic field did not increase significantly the intensity of the ^{1}H-NMR signals. A new Ir-*m*tppms-dihydride (*m*tppms = monosulfonated triphenylphosphine) was synthesized which was found active in both *para*-hydrogenation and in the dehydrogenation of formic acid; the latter reaction plays important role in chemical hydrogen storage. The Ir(I)-NHC/*m*tppms catalyst also proved useful for hydrogen generation from aqueous solution of formate salts in flow reaction systems (in a microfluidic reactor). It was demonstrated that the volume of generated hydrogen could be regulated simply and dynamically by regulating the temperature. With the use of water-soluble catalysts we have developed a new method for glycan analysis based on reductive amination.

A scientific publication (to be submitted shortly to Chemistry – A European Journal) about the *para*-hydrogenation reactions in aqueous media is attached at the end of this report.

Conference participations

(supported by National Research, Development and Innovation Office **NKFI-1 PD115535**)

- G. Papp, H. Horváth, G. Ölveti, Á. Kathó, F. Joó: *Application of para-Hydrogen in hydrogenation reactions catalysed by Ru-, Rh- and Ir-complexes in aqueous media* - 4th CARISMA Meeting - Catalityc Routines for Small Molecule Activation, 20-24.03.2016. Ljubljana, Slovenia - *poster presentation*
- G. Papp – *Selective hydrogenation with water soluble transition metal-phosphine complex catalysts*, Bruckner termi előadás, MTA Szerves és Biomolekuláris Kémiai Bizottság, Előadói Ülése, 27.05.2016. Budapest, Hungary - *invited oral lecture* (in Hungarian)
- G. Papp, G. Ölveti, H. Horváth, Á. Kathó, F. Joó - *Connection between the ant (formica rufa) and the magnetic imaging - The catalytic activity of* cis,mer-*[IrH_2Cl(mtppms)$_3$] in aqueous media* - 50. Komplexkémiai Kollokvium 30.05-01.06.2016. Balatonvilágos, Hungary - *oral lecture* (in Hungarian)
- G. Papp, H. Horváth, G. Ölveti, Á. Kathó, F. Joó – *Carbon dioxide utilization in acidic aqueous media with Ir-catalysts* - XIV. International Conference on Carbon Dioxide Utilisation, 11-15.09.2016. Sheffield, England - *poster presentation*
- G. Papp, H. Horváth, G. Ölveti, Á. Kathó, F. Joó – *Application of* para-*Hydrogen in hydrogenation reactions catalysed by Ru-, Rh- and Ir-complexes in aqueous media* - Being Smart In Coordination Chemistry: Medical Applications - LeStudium – Loire Valley Institute for Advanced Studies, 26-28.09.2016. Orleans, France - *invited oral lecture*
- F. Joó, Á. Kathó, A. Bényei, R. Gombos, H. Horváth, G. Papp, M. Purgel, A. Udvardy, K. Ősz, Á. Bertók, E. Bolyog-Nagy, P. P. Fehér, V. Kiss – *Catalysis and hydrogen storage* - Koordinációs Kémiai Munkabizottság ülés, Balatonvilágos, 2017. 05.30. - *oral lecture* (in Hungarian)
- G. Papp, H. Horváth, G. Ölveti, Á. Kathó, F. Joó: *CO_2 hydrogenation in aqueous solutions with water soluble Ir-catalysts* - 15th International Conference on Carbon Dioxide Utilization – ICCDU XV Shanghai, July 17-21, 2017 - *poster presentation*
- H. Horváth, G. Papp, H. Kovács, Á. Kathó, F. Joó: *Regulated hydrogen generation and storage in aqueous media with use of an Ir-NHC-phosphine complex catalyst in flow reactor* - 6th Conference on Frontiers in Organic Synthesis Technology Budapest, October 18-20, 2017 - *poster presentation*
- G. Ölveti, H. Horváth, Á. Kathó, F. Joó, G. Papp: *A* cisz,mer-*[IrH_2Cl(mtppms)$_3$] alkalmazása homogénkatalitikus CO_2 redukcióban* - 52. Komplexkémiai Kollokvium, 2018. május 22-24, Balatonvilágos – *oral lecture* (in Hungarian)
- G. Papp, H. Horváth, G. Ölveti, Á. Kathó, F. Joó: *CO_2 Hydrogenation in Aqueous Solutions with Water Soluble Ir-Catalysts* - 28th International Conference on Organometallic Chemistry (ICOMC2018), Florence (Italy), 15-20/7/2018 – *oral lecture*

Other conference participations

(acknowledgements include „National Research, Development and Innovation Office **NKFI-1 PD115535**")
- H. Horváth, G. Papp, G. Ölveti, Á. Kathó, F. Joó - *An efficient chemical hydrogen battery*, 4th CARISMA Meeting - Catalityc Routines for Small Molecule Activation, 20-24.03.2016. Ljubljana, Slovenia - *poster presentation*
- H. Horváth, G. Papp, H. Kovács, Á. Kathó, F. Joó - *Hydrogen battery-hydrogen storage with Ir-NHC-phosphine complexes in aqueous media* - 50. Komplexkémiai Kollokvium 30.05-01.06.2016. Balatonvilágos, Hungary - *oral lecture* (in Hungarian)

- V. Forgács, H. Horváth, G. Papp, Á. Kathó, F. Joó - *Deuteration, formation of ethers and esters with* $[Ru(H_2O)_6]^{2+}$ *catalyst* - 50. Komplexkémiai Kollokvium 30.05-01.06.2016. Balatonvilágos, Hungary - *oral lecture* (in Hungarian)

- H. Horváth, G. Papp, H. Kovács, Á. Kathó, F. Joó – *Efficient chemical hydrogen storage in aqueous media with use of Ir-NHC-phosphine complex catalysts* - XIV. International Conference on Carbon Dioxide Utilisation, 11-15.09.2016. Sheffield, England - *poster presentation*

- H. Horváth, G. Papp, H. Kovács, Á. Kathó, F. Joó - *Efficient chemical hydrogen storage in aqueous media with use of Ir-catalysts* - COST Action CM1205 – CARISMA Lisbon, March 6th-8th, 2017 - *poster presentation*

- G. Papp, H. Horváth, G. Ölveti, Á. Kathó, F. Joó: *Carbon dioxide utilization in acidic aqueous media* - COST Action CM1205 – CARISMA Lisbon, March 6th-8th, 2017 - *oral* (short communication, english) + *poster presentation*

- H. Horváth, G. Papp, H. Kovács, Á. Kathó, F. Joó - *Regulated hydrogen generation and storage in aqueous media with use of an Ir-NHC-phosphine complex catalyst in flow reactor* - 15th International Conference on Carbon Dioxide Utilization – ICCDU XV Shanghai, July 17-21, 2017 - *poster presentation*

- H. Horváth, G. Papp, H. Kovács, M. Purgel, P. Fehér, Á. Kathó, F. Joó - *Efficient reversible chemical hydrogen storage – towards a viable practical device* - 28th International Conference on Organometallic Chemistry (ICOMC2018), Florence (Italy), 15-20/7/2018 – *poster presentation*

- Á. Kathó, G. Ölveti, Gy. Hankó, R. Márton, A. Udvardy, F. Joó, G. Papp - *Catalytic Activity of* cis,mer-$[IrH_2Cl($m*tppms*$)_3]$ *in Hydrogenation and H-transfer Reactions* - 21st International Symposium on Homogeneous Catalysis (ISHCXXI), Amsterdam (Netherlands), 8-13/7/2018 – *poster presentation*

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

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Abstract: Biocompounds obtained in catalytic hydrogenations with *para*-H_2 may show strong *para*-hydrogen induced polarization (PHIP). Such hyperpolarized probe molecules are under intense screening as they may enable the application of the Magnetic Resonance Imaging (MRI) diagnostic modality for metabolism imaging. Here we report several water-soluble Rh(I)- and Ir(I)-complexes with N-heterocyclic carbene (NHC) and/or tertiary phosphine ligands which efficiently catalyze the synthesis of hyperpolarized compounds by *para*-hydrogenation in aqueous media.

Introduction

The use of ***p**ara*-**h**ydrogen **i**nduced **p**olarization (PHIP) was introduced into the field of catalysis by Bowers and Weitekamp in 1986.[1,2] 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-atoms in the ^{13}C-spectra and this sensitization gives a chance to recognize 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. The PHIP experiment has two different techniques, one of them is the PASADENA[4] when the reduction is performed in a strong magnetic field (within the NMR device) and the other is the ALTADENA[5] approach when the polarization transfer happens at the earth's magnetic field (outside the NMR device). 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.

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

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,[6] namely with the use of $[Rh(I)(norbornadiene)(THP)_2]^+[BF_4]^-$ where the THP stands for a monodentate phosphine ligand tris(hydroxymethyl)phosphine.[7] Such cationic Rh(I)-complexes with monodentate or bidentate phosphine ligands were applied as *para*-hydrogenation catalysts also in other reactions to induce PHIP in aqueous media.[8] Magnetically enhanced molecules were prepared in the gas phase from volatile substrates such as e.g. propyne and propene by heterogeneous hydrogenation with catalysts such as Pt/Al_2O_3,[9] immobilized Rh- and Ir-complexes[10] or silica-supported organometallic vanadium oxo complexes.[11] Hyperpolarized succinic-acid[12] or pyruvate[13] which allow metabolic imaging were synthetized by a yet another approach. In these cases, *para*-hydrogenation of maleic anhydride or 2-propynyl-2-oxopropanoate were conducted in organic solutions with a $[Rh(cod)(dppb)][BF_4]$ catalyst (dppb = 1,4-bis(diphenylphosphino)butane, cod = (1,5-cyclooctadiene)], and the water-soluble hyperpolarized target molecules were obtained by post-hydrogenation modifications, such as hydrolysis. Very recently Münnemann and co-workers showed a procedure for preparation of hyperpolarized fumarate via PHIP by using $[Cp^*Ru(CH_3CN)_3]PF_6$-complex as an appropriate catalyst.[14]

As can be seen from this brief overview, the choice of hydrogenation catalysts suitable for PHIP applications is rather limited both by mechanistic requirements[1,2] and by solubility properties. Ionic Rh(I)[6] and Ru(II)[14] 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.[15] Some of them were successfully applied for the hydrogenative modification of biological membranes not only in model systems but also in live cells, demonstrating also their sufficient biocompatibility.[15i,j] In this work we show that several water-soluble catalysts can be used advantageously for *para*-hydrogenation of water-soluble substrates i.e. 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 MRI of living systems (from cells to higher organisms).

Results and Discussion

Earlier research in our laboratory and elsewhere on water-soluble Ru(II)-, Rh(I)- and Ir(I)-tertiary phosphine complexes resulted in a large number of active and selective catalysts for

the hydrogenation of unsaturated substrate molecules in water or in water-organic two-phase solvent systems.[15] Here we report the application of several new water-soluble Rh(I)- and Ir(I)-catalysts for *para*-hydrogenation reactions in aqueous media, successfully applied for the preparation of spin-labelled products and molecules suitable for metabolic imaging.

The actual catalysts for *para*-hydrogenation were prepared in situ, by reactions of *m*tppms or *m*tppts with appropriate Rh(I)- and Ir(I)-precursors, such as [{RhCl(cod)}$_2$], [{IrCl(cod)}$_2$], [RhX(cod)(NHC)], and [IrX(cod)(NHC)], where X= Cl^- or OH^-, cod=1,5-cyclooctadiene, NHC=1,3-dialkyl- or 1,3-diarylimidazole-2-ylidene (Table 1). Enhanced aqueous solubility of these complexes is the result of the coordination of sulfonated monodentate tertiary phosphine ligands, such as *m*tppms[16] (monosulfonated triphenylphosphine) or *m*tppts[17] (trisulfonated triphenylphosphine) (Figure 1). In addition, *cis,mer*-[IrH$_2$Cl(*m*tppms)$_3$][c] was also used the first time as catalyst in PHIP studies in water.

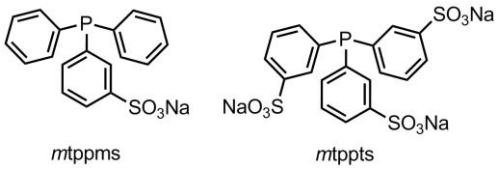
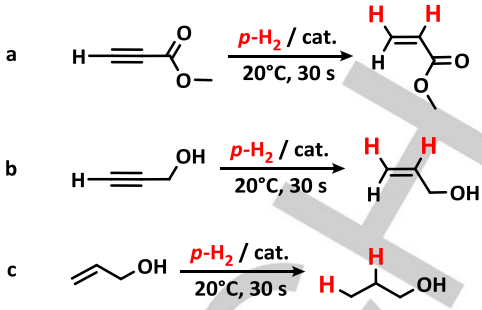


Figure 1. Water soluble phosphine ligands.

In this study, we investigated the *para*-hydrogenation of three subtrates: methyl propynoate (one of the most widely used substrates for PHIP studies), propargyl alcohol, and allyl alcohol. 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 Iridium N-heterocyclic carbene and carbene/phosphine 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.[20]

In general, complexes with *m*tppts ligand were not sufficiently soluble in pure alcohols, so their reactions were studied only in water and in water:methanol=9:1 mixtures. However, *m*tppms is soluble in MeOH and its in situ reaction with [{RhCl(cod)}$_2$] or [{IrCl(cod)}$_2$] afforded an active hydrogenation catalyst (Scheme1-**a** and Table 1, entries 1-2).

As a result of *para*-hydrogen addition to methyl propynoate, the special shape of polarized ^{1}H-NMR signals of methyl acrylate were detected confirming the hyperpolarization. With both catalysts approximately 3 min lifetime of polarization could be detected.



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

Similarly, most of the catalytic systems listed in Table 1 proved suitable for *para*-hydrogenation in aqueous media both with propargyl alcohol (Scheme1-**b**) and allyl alcohol (Scheme1-**c**) as substrates.

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)}$_2$] + *m*tppms[b]	**+**	**+**
2	[{IrCl(cod)}$_2$] + *m*tppms[b]	**+**	**+**
3	[{RhCl(cod)}$_2$] + *m*tppts	**+**	**+**
4	[{IrCl(cod)}$_2$] + *m*tppts	**+**	**+**
5	[IrCl(cod)(bmim)] + *m*tppms	**+**	**-**
6	[IrCl(cod)(bmim)]+*m*tppts	**+**	**-**
7	[IrCl(cod)(emim)] + *m*tppms	**+**	**-**
8	[IrCl(cod)(emim)] + *m*tppts	**+**	**-**
9	[RhCl(cod)(IMes)] + *m*tppms	**+**	**+**
10	[RhCl(cod)(IMes)] + *m*tppts	**+**	**+**
11	[RhOH(cod)(IMes)] + *m*tppms	**+**	**-**
12	[RhOH(cod)(IMes)] + *m*tppts	**+**	**+**
13	[RhOH(cod)(iPr)] + *m*tppms	**+**	**-**
14	[RhOH(cod)(iPr)] + *m*tppts	**+**	**+**

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

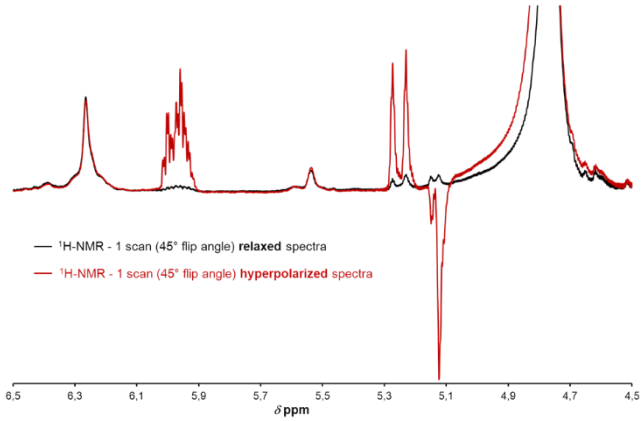


Figure 2. Hyperpolarized and relaxed ^{1}H-NMR spectra of *para*-hydrogenated propargyl alcohol. [RhOH(cod)(iPr)] = 25 mM; [*m*tppms] = 75 mM; [propargyl alcohol] = 200 mM; $P_{para\text{-}H2}$ = 1.5-1.6 bar (*T*=77K) (~ 6 bar, *T*=293K); *V*(solvent) = 0.4 mL. (Table 1. entry 13)

The reactions were performed in 5 mm NMR tubes. As detailed in the Experimental, the reaction protocol consists 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, c)thawing the sample and performing the *para*-hydrogenation, d)^{1}H-NMR detection of the products. The hyperpolarized allyl alcohol (Scheme 1- **b**) and propanol (Scheme 1-**c**) were detected by ^{1}H-NMR spectroscopy with 45° flip angle measurements (Figure 2 and Table 1, entries 1-4).

Most of the water-soluble, catalytically active Rh- and Ir-complexes used in this study, contain coordinated N-heterocyclic carbene as well as sulfonated phosphine ligands.[19,15g] The propargyl alcohol is efficiently *para*-hydrogenated with these mixed ligand NHC/sulfonated triphenylphosphine Rh(I)- and Ir(I)-complexes – as shown by the polarised signals detected by normal ^{1}H-NMR spectroscopy with 45° flip angle and ^{1}H-NMR-OPSY[21] measurements (Table 1, entries 5-14). By performing the experiments in aqueous media the lifetime of polarized signals was found to be in the range of 1-3 minutes. In general, the aqueous solvents contained approximately 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.

The Rh(I)- Ir(I)-based catalyst precursors used in this study contain a coordinated 1,5-cyclooctadiene ligand which is transformed during prehydrogenation to free cyclooctane, a known biomembrane fluidizing agent. Recently we have synthesized a highly water-soluble, cod-free Ir(I)-*m*tppms hydrogenation catalyst, *cis,mer*-[IrH_2Cl(*m*tppms)$_3$], in the reaction of hydrated $IrCl_3$ and monosufonated triphenylphosphine.[22] (It is of interest that this complex is among the three best homogeneous catalysts for the selective decomposition of formic acid to hydrogen and carbon dioxide – a promising approach to H_2 storage/delivery.[23])

cis,mer-[IrH_2Cl(*m*tppms)$_3$] is sufficiently soluble also in methanol. 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 occured.

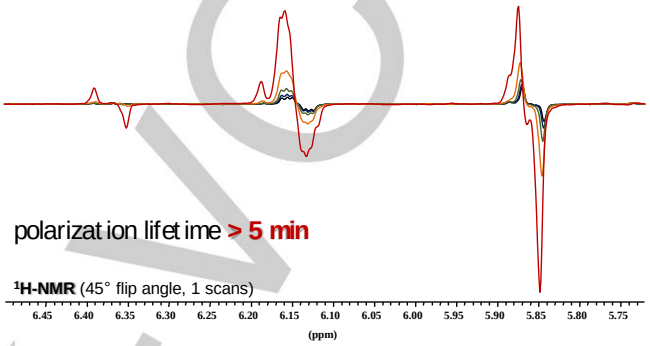


Figure 3. Hyperpolarized ^{1}H-NMR signals of *para*-hydrogenated methyl propynoate. [*cis,mer*-[IrH_2Cl(*m*tppms)$_3$]] = 25 mM; [methyl propynoate] = 200 mM; $P_{para\text{-}H2}$ = 1.6 bar (*T*=77K), (~6 bar, *T*=293K); *V*(solvent) = 0.4 mL.

The high catalytic activity of *cis,mer*-[IrH_2Cl(*m*tppms)$_3$] allows *para*-hydrogenation reactions not only in alcoholic solutions but also in plain water. For the hydrogenation of propargyl alcohol, the polarized signals and the changes in their intensities in time are shown in Figure 4.

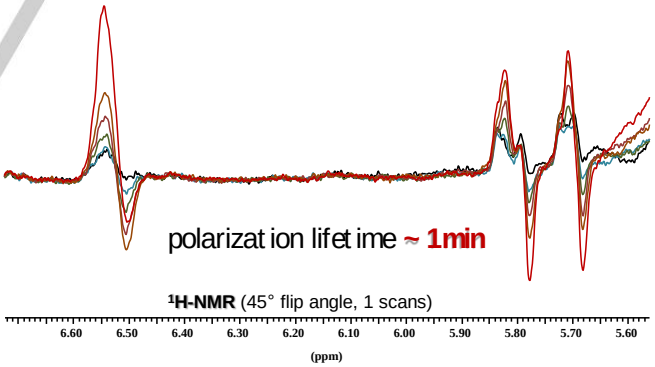


Figure 4. *Para*-hydrogenation of propargyl alcohol in aqueous media (water:methanol = 9:1). [*cis,mer*-[IrH_2Cl(*m*tppms)$_3$]] = 25 mM; [propargyl alcohol] = 200 mM; $P_{para\text{-}H2}$ = 1.6 bar (*T*=77K), (~6 bar, *T*=293K); *V*(solvent) = 0.4 mL.

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).

Conclusions

The use of water as 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 described examples of catalysts hitherto not used 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_2Cl(*m*tppms)$_3$]. With these catalysts, efficient *para*-hydrogenation of unsaturated alcohols could be realized in aqueous media. The hyperpolarized ^{1}H-NMR signals were detected for approximately 1-3 minutes when water used as a solvent and up to 5 minutes in methanol. These systems allow preparation 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) was prepared in the appropriate solvent 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. After that the solution containing the activated catalyst was placed into the 5 mm NMR tube equipped with Quick-Pressure valve. The substrate (200 mM) was added and the reaction vessel 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 the hydrogenation reaction. The NMR tube was then defrosted at room temperature and 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 after this step, the sample was placed into the NMR spectrometer and the hyperpolarized ^{1}H-NMR signals were recorded by 45° flip angle and OPSY measurements.[21]

Acknowledgments

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Keywords: *para*-hydrogen • PHIP • aqueous media • transition metal complexes • catalysis

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