

Aqueous Biphasic Hydrogenations

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ABSTRACT

In addition to the useful physical properties of biphasic systems (easy separation of products and catalyst, facile catalyst reuse) aqueous media may largely influence the chemistry of catalytic reactions. By appropriate pH manipulations, the selectivity of hydrogenation of unsaturated aldehydes with ruthenium(II) phosphine catalysts was controlled from the exclusive formation of saturated aldehydes to that of unsaturated alcohols. Phase separation of the constituents of catalytic systems eliminated substrate inhibition (hydrogenation of aldehydes) and helped formation of catalytically active species ($[\text{RhH}(\text{PPh}_3)_3]$ from $[\text{RhCl}(\text{PPh}_3)_3]$ in hydrogenation of acetophenone). The reactive nature of H_2O was revealed by fast catalysis of H/D exchange and deuteration processes.

Introduction

Homogeneous transition metal catalysis in solutions has much to offer with regard to activity and selectivity. The outstanding achievements in enantioselective catalysis have just recently been recognized by the year 2001 Nobel Prize in Chemistry. Of the long list of homogeneously catalyzed enantioselective reactions, only the hydrogenation of prochiral enamides and ketones, which can be carried out with practically 100% enantioselectivity using rhodium and ruthenium complexes of specially designed chiral phosphine, amine or other ligands, is mentioned here. Such a precision catalysis has far-reaching consequences on the design of green chemical processes, since it allows selective synthesis of the desired products with no contamination by useless or often toxic byproducts. In addition to its importance in fine chemicals synthesis, homogeneous transition metal catalysis is also practiced in production of bulk chemicals, exemplified by oligomerization, coordination polymerization and hydroformylation of alkenes, and many other processes. Nevertheless, a wider use of homogeneous catalysis is hampered by the

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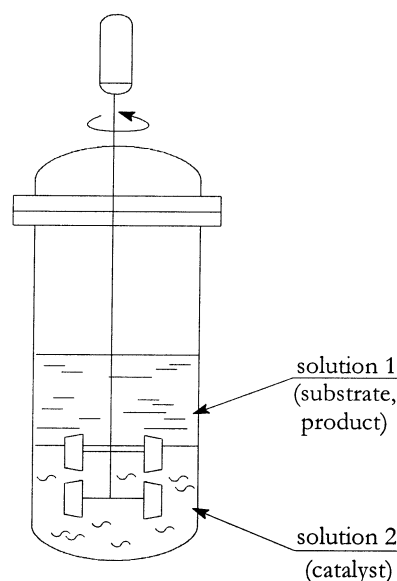


FIGURE 1. General arrangement for liquid biphasic catalysis.

difficulties of catalyst recovery and recycling with a simultaneous isolation of a catalyst-free product mixture. Catalyst–product separation can easily be achieved in heterogeneous catalysis; however, solid catalysts of the desired selectivity are simply not available for several important catalytic transformations.

Many attempts have been made to combine the activity and selectivity of soluble catalysts with the easy separation of their solid counterparts. Until now, however, immobilization on various solid supports has failed to produce catalysts that are stable, active, and selective enough (i.e., sufficiently economical) for large-scale applications. A more successful approach is in the use of immiscible liquid phases, of which one dissolves the catalyst and the other is composed of the substrate(s) and product(s) or their solution in a suitable solvent (Figure 1).^{1–3} Upon thorough mixing, the catalyst and the substrates react in the interphase region or in the catalyst-containing phase, provided the substrates have sufficient solubility in that phase. Consequently, the catalytic transformation can still be regarded as a homogeneous reaction with molecularly dispersed catalyst and substrates; however, by easy and well-known phase-separation techniques, the catalyst can be recovered (continuously recycled) in one of the liquid phases.

This method of liquid biphasic catalysis with a transition metal-based catalyst was first introduced to industry by Shell in its SHOP process for production of higher olefins by oligomerization of ethene.² In this particular case, both phases are *organic* solutions: the Ni-containing catalyst is dissolved in 1,4-butanediol, and the other phase is composed of the compressed ethene, also dissolving the product oligomers. Organic–organic biphasic procedures are still investigated in detail, and the possibilities are largely expanded by the recent introduction of the *fluorous*^{3a} biphasic systems in which one of the phases specifically is a perfluorinated alkane, amine, etc. Other

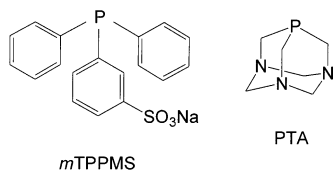


FIGURE 2. The structure of *m*-TPPMS and PTA.

unusual solvents such as supercritical fluids^{3b} and ionic liquids^{3c} have also come to the scene of liquid biphasic catalysis recently. Nevertheless, far less expensive and perhaps more akin to green chemical synthesis is the use of water as one of the immiscible phases.^{1,4} Our first paper on aqueous organometallic catalysis⁵ was published in 1973, the same year in which the idea of liquid biphasic catalysis¹ was suggested as a general means for heterogenizing homogeneous catalysts. Since then, an enormous effort has been put into the development of catalytic reactions in aqueous solutions and in biphasic mixtures of water with other solvents, the most outstanding achievement being the Ruhrchemie–Rhône Poulenc process for the industrial hydroformylation of propene.^{1b,2} These studies revealed several peculiarities of aqueous biphasic catalysis, and the present Account summarizes our results in this direction.

Water-Soluble Tertiary Phosphine Complexes of Transition Metals and the Hydrogenation of Olefins in Homogeneous Aqueous Solutions

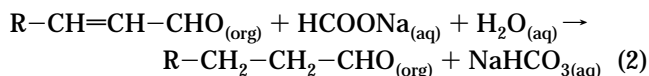
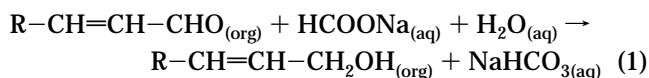
Recent aqueous organometallic catalysis relies heavily (although not exclusively) on the use of water-soluble tertiary phosphine ligands. The obvious reason comes from the most important role phosphine complexes play in catalysis in organic solutions and from the aim of creating closely similar catalytic systems working in aqueous media. Of the several hundreds of water-soluble phosphines investigated to the present, sulfonated triphenylphosphine derivatives have attracted the most interest because of their relatively easy synthesis. The sulfonate groups remain deprotonated and noncoordinating in a wide pH range. Consequently, the solubility and coordination properties of such ligands and their complexes are not influenced by variations in pH, in contrast to water-soluble phosphines with amino, hydroxyl or carboxylic functions. The reaction of triphenylphosphine with fuming sulfuric acid yields sulfonated derivatives with $-\text{SO}_3^-$ groups in meta positions, such as $\text{Ph}_2\text{P}(\text{C}_6\text{H}_4-3-\text{SO}_3\text{M})$, *m*-TPPMS,^{6a} (Figure 2); $\text{PhP}(\text{C}_6\text{H}_4-3-\text{SO}_3\text{M})_2$, *m*-TPPDS^{6b}; and $\text{P}(\text{C}_6\text{H}_4-3-\text{SO}_3\text{M})_3$, *m*-TPPTS,^{6b} usually isolated as alkali metal salts ($\text{M} = \text{Na}^+$ or K^+). Complexes of ortho- and para-sulfonated triphenylphosphines have also been applied in catalysis, as well as those of 1,3,5-triaza-7-phosphaadamantane (PTA), a small, aliphatic tertiary phosphine ligand (Figure 2).^{6c} One of the three nitrogens of this caged phosphine can be protonated ($\text{p}K_a = 6.0$); both PTA and PTAH^+ are very soluble in water, as are their metal complexes.

Reaction of $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ with an excess of *m*-TPPMS or PTA in refluxing ethanol provides $[\{\text{RuCl}_2-$

$(m\text{-TPPMS})_2\}_2]$,^{6a} $[\text{RhCl}(m\text{-TPPMS})_3]$,^{6a} $[\text{RuCl}_2(\text{PTA})_4]$, and $[\text{RhCl}(\text{PTA})_3]$.⁷ Using water or aqueous acids as solvents, these complexes were found to be active in hydrogenation of olefins either in solution (unsaturated acids, allyl alcohol) or in dispersion (1-hexene, styrene, unsaturated phospholipids).^{8,9} Hydrogenation of crotonic, maleic, and fumaric acids at 25–60 °C proceeded with typical turnover frequencies (TOF) of 100–700 h^{-1} (mol converted substrate/mol catalyst·h). These reaction rates and the basic kinetic features^{8,9} were found to be similar to those of olefin hydrogenations with the related $[\text{RuCl}_2(\text{PPh}_3)_3]$ and $[\text{RhCl}(\text{PPh}_3)_3]$ complexes.¹⁰ However, important differences between aqueous and organic solutions were also observed, and some of these are discussed below.

Biphasic Transfer Hydrogenation of Aldehydes

Various aldehydes were found to undergo reduction to the corresponding alcohols (eq 1) by hydrogen transfer from sodium formate catalyzed by $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$ (with excess *m*-TPPMS),¹¹ as well as by $[\text{RuCl}_2(\text{PTA})_4]$.⁷ The results in Table 1 demonstrate the efficiency of both catalysts. Despite the need for mass transfer from the organic phase to the aqueous one, initial turnover frequencies with $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$ were generally $> 100 \text{ h}^{-1}$, and with $[\text{RuCl}_2(\text{PTA})_4]$, $> 15 \text{ h}^{-1}$. However, 2-hydroxyaldehydes (salicylaldehyde, 2-hydroxy-1-naphthaldehyde) were not reduced. Most notably, hydrogen transfer reduction of all unsaturated aldehydes afforded unsaturated alcohols with 100% selectivity. Literature reports showed the same selectivity of Ru–*m*-TPPTS catalysts with H_2 as the hydrogen source.¹² In contrast, $[\text{RhCl}(m\text{-TPPMS})_3]$ and $[\text{RhCl}(\text{PTA})_3]$ showed negligible activity in hydrogenation of the aldehyde function; however, they efficiently catalyzed the formation of saturated aldehydes (eq 2).



In these genuine biphasic reactions, the catalyst and the reducing agent are dissolved in the aqueous phase while the aldehyde is in the organic phase, either neat or dissolved in a water-immiscible solvent. The reaction rates are somewhat lower but comparable to those in the analogous phase transfer catalytic (PTC) system (see Figure 3), having the catalyst $[\text{RuCl}_2(\text{PPh}_3)_3]$, the substrate, and products in the organic phase, and employing a quaternary ammonium formate to facilitate the transfer of HCOO^- from the aqueous to the organic phase.¹³ Nevertheless, the data of Table 1 also illustrate the general problem of liquid–liquid biphasic catalysis: under identical conditions, the extent of hydrogenation of butanal, pentanal, and hexanal decreases substantially with their decreasing solubility in the catalyst-containing aqueous phase. The reactions are inhibited by an excess of the substrate;^{7,11} therefore, the reaction rates go through a maximum with increasing aldehyde concentration (Figure

Table 1. Catalytic Reduction of Aldehydes with Hydrogen Transfer from Aqueous HCOONa

substrate	yield of alcohol, % ^a	
	[Ru- <i>m</i> TPPMS] ^b	[Ru-PTA] ^c
benzaldehyde	99.7	64.0
4-methylbenzaldehyde	99.5	23.6
4-methoxybenzaldehyde	98.8	26.7
4-bromobenzaldehyde	99.8	16.3
2-naphthaldehyde	100	n.d. ^d
salicylaldehyde	0	0
butanal	n.d.	72.8
pentanal	n.d.	46.1
hexanal	n.d.	23.0
2-butenal ^e	78 ^f	87.6
citral ^{e,g}	98	n.d.
citronellal ^e	93	n.d.
cinnamaldehyde ^e	98	21.2

^a Determined by gas chromatography. ^b 0.005 mmol of $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$; 0.1 mmol of *m*-TPPMS; 1 mmol of aldehyde (neat); 3 mL of 5 M HCOONa in water; 80 °C; reaction time, 1.5–7 h. ^c 0.0625 mmol of $[\text{RuCl}_2(\text{PTA})_4]$; 1.35–6.93 mmol of aldehyde in 5 mL of chlorobenzene; 5 mL of 5 M HCOONa in water; 80 °C; reaction time, 3 h. ^d Not determined. ^e Exclusive formation of unsaturated alcohols. ^f At 30 °C, isolated yield. ^g Mixture of geraniol and neral 2:1; no isomerization was observed.

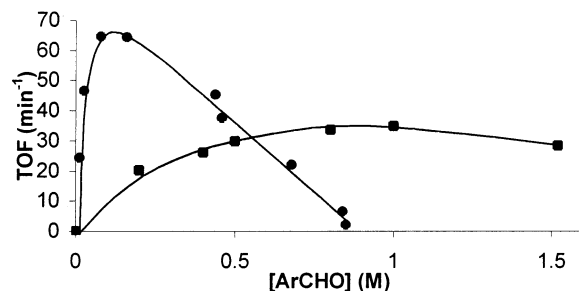


FIGURE 3. Initial rates of the transfer hydrogenation of *p*-tolualdehyde¹³ (●, $[\text{RuCl}_2(\text{PPh}_3)_3]$, 50 °C, with phase transfer catalysis) and benzaldehyde¹¹ (■, $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2] + m\text{-TPPMS}$, 80 °C, biphasic) by aqueous HCOONa.

3). In the PTC variant, in which the catalyst and the substrate are found in the same phase, this maximum is sharp, and the rate falls back to zero at relatively low aldehyde concentrations. For practically useful reaction rates, one must keep the aldehyde concentration low by dilution with an organic solvent. Conversely, because of the limited solubility of aldehydes in aqueous HCOONa solutions, the $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$ or $[\text{RuCl}_2(\text{PTA})_4]$ catalysts remain active even when the organic phase is composed of neat substrate. This is a clear example of what is termed “protection by phase separation”, but in this case, it is the catalyst that is protected against substrate inhibition. At the end of the reaction, the organic phase of the product and the catalyst-containing aqueous phase can be easily separated. Elimination of the need of an organic solvent, simple catalyst recycling, and the mild conditions of isolation of the product with no contamination by the catalyst are valuable *green* features of this biphasic reduction of aldehydes.

Effect of pH on the Selectivity

Selective reduction of unsaturated aldehydes to unsaturated alcohols, as discussed above, is a rather unusual

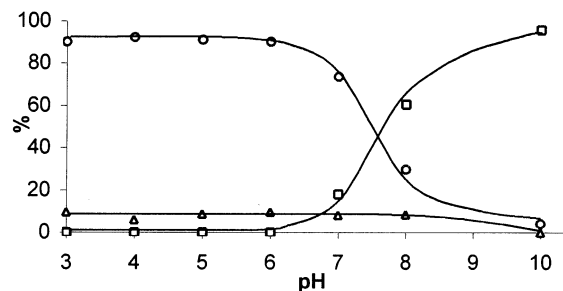
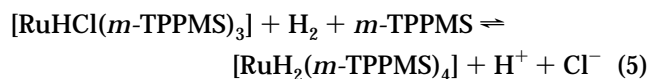
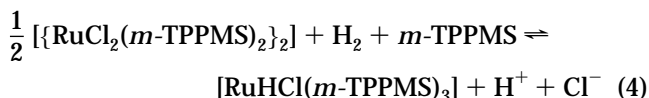
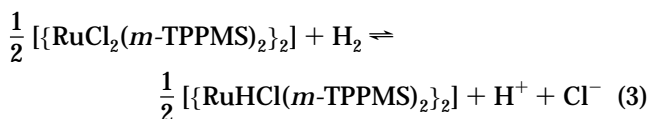


FIGURE 4. Mole fraction of $[\text{RuHCl}(m\text{-TPPMS})_3]$ (○), $[\text{RuH}_2(m\text{-TPPMS})_4]$ (□) and $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$ (△) as a function of pH, determined by ¹H and ³¹P NMR spectroscopy. $[\text{Ru}] = 2.4 \times 10^{-2}$ M, $[m\text{-TPPMS}] = 7.2 \times 10^{-2}$ M, 0.2 M KCl, 50 °C, H₂, $P_{\text{total}} = 1$ bar. Reproduced with permission from ref 15a. Copyright 1998, Wiley-VCH.

finding for several reasons. First, there are only a few homogeneous catalysts that are selective for the hydrogenation of an aldehyde in the presence of an olefinic bond.¹⁰ Second, $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$ is an active catalyst for C=C hydrogenation in olefinic acids.^{8,9} Furthermore, $[\text{RuCl}_2(\text{PPh}_3)_3]$ is known to catalyze the hydrogenation of olefins with hydrogen transfer from mixtures of HCOOH and alkali metal formates.¹⁴ The rationale of this apparent contradiction was found in the effect of pH on the formation of various hydridophosphine complexes of Ru(II).

Reaction of $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$ and H₂ in aqueous solutions in the presence of excess *m*-TPPMS is accompanied by color changes and proton production. We have studied these processes in detail both by pH potentiometry and simultaneous ¹H and ³¹P NMR investigations.¹⁵ The experiments revealed the formation of various Ru(II) hydrides (eq 3–5).



Note that although formation of analogous hydride complexes from $[\text{RuCl}_2(\text{PPh}_3)_3]$ in apolar organic solvents requires the presence of a base (Et₃N, 1,8-diaminonaphthalene, etc.),¹⁰ in aqueous solutions, water itself plays the role of a proton acceptor. Equilibria 3–5 are governed by the actual concentration of hydrogen; therefore, the distribution of ruthenium in the various hydrides is strongly pH-dependent. In an excess of *m*-TPPMS, $[\{\text{RuHCl}(m\text{-TPPMS})_2\}_2]$ is a minor species, whereas $[\text{RuHCl}(m\text{-TPPMS})_3]$ and $[\text{RuH}_2(m\text{-TPPMS})_4]$ are almost exclusively formed in strongly acidic and in strongly basic solutions, respectively (Figure 4).

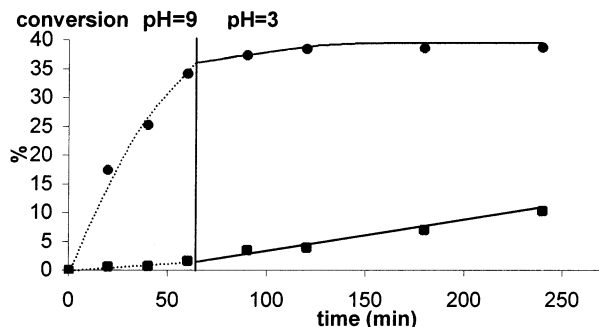


FIGURE 5. Selectivity of the hydrogenation of cinnamaldehyde to cinnamyl alcohol (●) and dihydrocinnamaldehyde (■) as a function of pH. Conditions: 50 μL of cinnamaldehyde, 10 mg of $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$, 12 mg of $[m\text{-TPPMS}]$, 5 mL of chlorobenzene, 3 mL of 0.2 M KCl buffered with $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4/\text{HCl}$, 80 $^\circ\text{C}$, H_2 , $P_{\text{total}} = 1$ bar. Reproduced with permission from ref 15a. Copyright 1998 Wiley-VCH.

As established earlier,⁸ the active species for olefin hydrogenation is $[\text{RuHCl}(m\text{-TPPMS})_2]$, formed in acidic solutions by phosphine dissociation from $[\text{RuHCl}(m\text{-TPPMS})_3]$, and therefore, the rate of $\text{C}=\text{C}$ hydrogenation decreases with increasing concentration of $m\text{-TPPMS}$. Conversely, $[\text{RuH}_2(m\text{-TPPMS})_4]$ was found to be a selective catalyst for the reduction of aldehydes. The reason for this selectivity most probably is in the coordinative saturation of $[\text{RuH}_2(m\text{-TPPMS})_4]$, which prevents the coordination of a $\text{C}=\text{C}$ bond but allows the hydrogenation of aldehydes by intermolecular nucleophilic hydride transfer. Catalysis by a coordinatively saturated Ru species is also corroborated by the lack of inhibition by excess phosphine; in fact excess $m\text{-TPPMS}$ increases the reaction rate, probably because of its surfactant (hence, aldehyde solubilizing) effect.¹¹ (Interestingly, the catalytic activity of $\text{Ru}-m\text{-TPPMS}$ and $\text{Ru}-\text{PTA}$ complexes in the formate reduction of aldehydes is influenced in a sharply different way by an excess of the phosphine ligand. Unlike $m\text{-TPPMS}$, excess PTA inhibits the reaction,⁷ and when prepared from $[\text{Ru}(\text{H}_2\text{O})_6](\text{tos})_2 + \text{PTA}$ ($\text{tos} = 4\text{-toluenesulfonate}$), the catalyst shows a maximum activity at $[\text{PTA}]/[\text{Ru}] = 3$. The easy formation of $[\text{RuH}(\text{PTA})_5]^+$ may contribute to the decrease of reactivity at high PTA concentrations; a similar pentakisphosphino complex is not formed with the bulky $m\text{-TPPMS}$ ligand.¹⁶)

Since the same $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2] + m\text{-TPPMS}$ precatalyst can yield either $[\text{RuHCl}(m\text{-TPPMS})_3]$ or $[\text{RuH}_2(m\text{-TPPMS})_4]$ in acidic or in basic aqueous solutions, respectively, the selectivity of the reduction of unsaturated aldehydes can be switched from $\text{C}=\text{O}$ to $\text{C}=\text{C}$ reduction by simple pH manipulations. Figure 5 shows an example, when hydrogenation of cinnamaldehyde at pH 9 resulted in formation of cinnamyl alcohol; however, upon acidification to pH = 3 the same reaction mixture afforded 3-phenylpropanal as the major product.

It is not at all surprising that $\text{Ru}(\text{II})$ complexes with para-monosulfonated triphenylphosphine ligands show reactivity closely related to that of their $m\text{-TPPMS}$ -containing analogues. Nevertheless, para sulfonation results in a considerably smaller steric bulk, as shown by

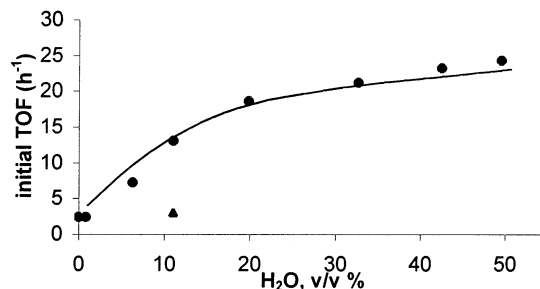


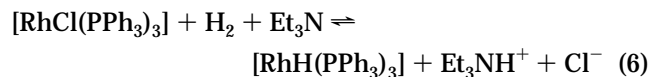
FIGURE 6. Initial rate of the biphasic hydrogenation of acetophenone as a function of the relative amount of the aqueous phase: water (●) or 0.5 M $[\text{Et}_3\text{N}\cdot\text{HCl}]$ (▲). $[\text{RhCl}(\text{PPh}_3)_3] = 2.0 \times 10^{-2}$ M, $[\text{substrate}]/[\text{catalyst}] = 435$, $[\text{Et}_3\text{N}]/[\text{Rh}] = 2$, 50 $^\circ\text{C}$, H_2 , $P_{\text{total}} = 1$ bar.

the respective Tolman cone angles: $p\text{-TPPMS}$, 137.7 $^\circ$ and $m\text{-TPPMS}$, 177.6 $^\circ$. As a consequence, formation of the tetrakisphosphino species $[\text{RuH}_2(p\text{-TPPMS})_4]$ can be observed already in slightly acidic solutions (its mol fraction at pH 6 is $\sim 20\%$, as compared to $\sim 0\%$ for $[\text{RuH}_2(m\text{-TPPMS})_4]$), and the shift of selectivity from $\text{C}=\text{C}$ to $\text{C}=\text{O}$ bond hydrogenation in cinnamaldehyde also starts at lower pH ($\sim \text{pH } 3$).¹⁷

The selectivity observed in the ruthenium-catalyzed transfer hydrogenation of aldehydes with aqueous formate solutions can be easily rationalized now by recalling that the pH of the routinely used 5 M sodium formate solutions is 7.8 and slightly increases with increasing conversion (NaHCO_3 formation). At this pH, the dominant species is $[\text{RuH}_2(m\text{-TPPMS})_4]$, which leads to exclusive formation of unsaturated alcohols.

Hydrogenation of Acetophenone in Aqueous Biphasic Systems Catalyzed by $[\text{RhCl}(\text{PPh}_3)_3]$

Wilkinson's catalyst is not active in hydrogenation of ketones; however, in the presence of suitable bases, such reactions may take place.^{10,18} Although in hydrogenation of acetophenone both the substrate and the catalyst are insoluble in water, we observed that the presence of a separate aqueous phase still resulted in a substantial acceleration of hydrogenation, and the reaction rate increased with increasing volume of the aqueous phase (Figure 6).¹⁹ An efficient reaction required the presence of a base (Et_3N or 1,5-diazabicyclo[4.3.0]non-5-ene). Prepared from $[\{\text{RhCl}(\text{COD})\}_2] + n\text{PPh}_3$, the catalyst's activity showed a distinct maximum at $[\text{P}]/[\text{Rh}] = 3$. These phenomena can be rationalized by assuming the real catalytic species is $[\text{RhH}(\text{PPh}_3)_3]$, formed according to eq 6.



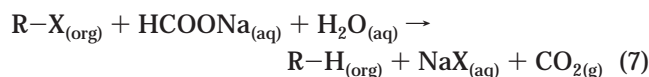
In homogeneous organic solutions, this equilibrium can be made complete with an excess of NEt_3 . However, in water-benzene mixtures, triethylamine hydrochloride dissolves preferentially in the aqueous phase, shifting the equilibrium toward the formation of $[\text{RhH}(\text{PPh}_3)_3]$. Indeed,

under the conditions of Figure 6, up to 85% of chloride was found in the aqueous phase by titration with $\text{Hg}(\text{NO}_3)_2$. Below its solubility limit, water itself has no effect; however, increasing its volume relative to that of benzene facilitates the distribution of more and more Cl^- into the aqueous phase, thereby increasing the concentration of $[\text{RhH}(\text{PPh}_3)_3]$ in the organic phase, resulting in higher rates of hydrogenation. This suggestion is also supported by the finding that when a 0.5 M $\text{Et}_3\text{N}\cdot\text{HCl}$ solution was used as the aqueous phase, no increase of the rate was produced (Figure 6). Aqueous–organic biphasic systems are superior to the widely used methanol or benzene–ethanol mixed solvents in that there are no hydroxide or alkoxide ions in the organic phase that could lead to the formation of hydroxo- or alkoxorhodium complexes.

Base dehydrochlorination^{20a} of neutral $[\text{RhH}_2\text{XL}_n]$ and deprotonation^{20b} of cationic $[\text{RhH}_2\text{S}_x\text{L}_n]^+$ (S = solvent) complexes play important roles in catalysis, and in aqueous solutions, these can be also finely tuned with careful manipulation of pH. By combined pH potentiometry and ^1H and ^{31}P NMR measurements, we have shown that hydrogenation of $[\text{RhCl}(m\text{-TPPMS})_3]$ affords either $[\text{RhH}_2\text{-Cl}(m\text{-TPPMS})_3]$ or $[\text{RhH}(m\text{-TPPMS})_3(\text{H}_2\text{O})]$ below and above pH 8.2, respectively.²¹ Formation of the important hydroformylation (pre)catalyst, $[\text{RhH}(\text{CO})(m\text{-TPPMS})_3]$ from $[\text{RhCl}(\text{CO})(m\text{-TPPMS})_2]$, $m\text{-TPPMS}$, and H_2 is also strongly pH-dependent: no reaction takes place below pH 5, and the reaction nears completion only above pH 9. Such equilibria may contribute to the known increase of the rate of hydroformylations with increasing pH in aqueous biphasic systems.²²

Dehalogenation of Organic Halides by Catalytic Hydrogen Transfer from Aqueous HCOONa

An important problem in environmental protection is the dehalogenation of organic halides, which is often effected by catalytic hydrogenolysis of the relevant $\text{C}-\text{X}$ bonds. We have found that $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2] + m\text{-TPPMS}$ and $[\text{Ru}(\text{H}_2\text{O})_3(\text{PTA})_3](\text{tos})_2$ were suitable catalyst precursors for hydrodehalogenation of organic halides with sodium formate as the hydrogen source (eq 7 and Table 2).²³



Carbon tetrachloride, chloroform, and benzyl chloride were highly susceptible to hydrogenolysis; however, hydrodehalogenation of dichloromethane was not observed. Hexyl and cyclohexyl halides reacted slowly, showing the expected order of reactivity ($\text{I} > \text{Br} > \text{Cl}$). Chlorobenzene could not be dehalogenated. Radical scavengers slowed the reaction of CCl_4 but did not stop it completely. The reaction proceeds with much inferior rates when H_2 is used as the hydrogen source. As an example, under the conditions of Table 2, only 2% conversion of CCl_4 to CHCl_3 was detected under 5 bar H_2 , instead of 55% with HCOONa (reaction time, 3 h). Aqueous solutions of HCOONH_4 , $\text{HCOONa} + \text{HCOOH}$ (1:1), and Na_2HPO_4 could

Table 2. Catalytic Dehalogenation of Organic Halides with Hydrogen Transfer from Aqueous HCOONa

substrate	initial rate, h^{-1} ^a	
	$[\text{Ru}-m\text{TPPMS}]^b$	$[\text{Ru}-\text{PTA}]^c$
carbon tetrachloride	478	88
chloroform	80	6
benzyl chloride	291	n.d. ^d
1-Cl-hexane	3	46
1-Br-hexane	10	56
1-I-hexane	68	86
Cl-cyclohexane	2	5
Br-cyclohexane	16	10
chlorobenzene	0	0

^a Turnover frequency: mol converted substrate/mol catalyst·h, determined by gas chromatography. ^b 5.5×10^{-3} mmol of $[\{\text{RuCl}_2(m\text{-TPPMS})_2\}_2]$, 0.05 mmol of $m\text{-TPPMS}$, 8 mmol of substrate, 25 mmol of HCOONa , 15 mL of water, 80 °C. ^c 5×10^{-3} mmol of $[\text{Ru}(\text{H}_2\text{O})_3(\text{PTA})_3](\text{tos})_2$, 8 mmol of substrate; 25 mmol of HCOONa , 5 mL of water, 80 °C. ^d Not determined.

also be used; however, in the latter two cases, the hydrogen donors were partially decomposed (as shown by increased reactor pressures), and somewhat diminished yields of CHCl_3 were obtained (28% and 31%, respectively). In the case of HCOOH , a fast catalytic decomposition occurred that prevented efficient hydrodehalogenation (CHCl_3 yield 4%).

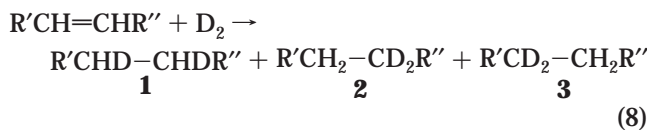
These biphasic hydrodehalogenations utilizing HCOONa as the H source proved more efficient than the related processes catalyzed by $[\text{RuCl}_2(\text{PPh}_3)_3]$ in homogeneous organic solutions (CCl_4 , xylene–ethanol, H_2 , 25 °C: 64 catalyst turnovers in 5 days; $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$, dioxane, HCOOLi , reflux: 26 turnovers in 6 h).²⁴ In addition, the aqueous–organic biphasic approach allows the separation of the water-soluble catalyst from the organic products, albeit the process is biased by a relatively fast catalyst deactivation²³ and by the accumulation of HX or halide salts in the aqueous phase.

Deuteration of Lipid Dispersions Using D_2O as Deuterium Source and the Catalysis of H/D Exchange in Water

Aqueous dispersions of phospholipids (liposomes) are microheterogeneous biphasic systems that are often used as synthetic models of biomembranes. Soybean lecithin, one of the most readily available phospholipids, contains large proportions of linoleic (59%) and linolenic (8%) acid residues (18-carbon fatty acids with two and three $\text{C}=\text{C}$ bonds, respectively). Catalytic hydrogenation of the unsaturated acyl moieties within such liposomes was studied with several catalysts²⁵ in order to get more insight into the details of the hydrogenation of native biomembranes (in many case, those of living cells). Hydrogenation²⁶ or cis-to-trans isomerization²⁷ of the $\text{C}=\text{C}$ bonds in membrane lipids results in controlled alterations of the membrane physical state. Therefore, this method gives a unique possibility of studying the relation of membrane fluidity to the functioning of various enzymes and the ability of living organisms to tolerate environmental stress (sudden changes in temperature, osmotic pressure, etc.).^{1a,25} However, our studies also shed some light on the mechanism

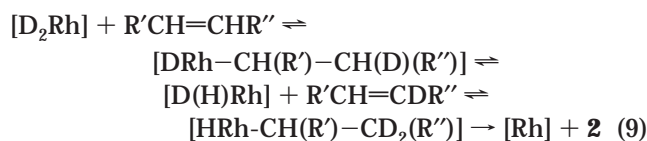
of hydrogenations by the respective catalysts in these unusual reaction mixtures.

When liposomes of soybean lecithin (1 mg/mL) were prepared in phosphate buffer (pH = 4.70) and hydrogenated (H₂, 1 bar) using the [RhCl(PTA)₃] catalyst (1 mM), 34% of all double bonds were saturated in 40 min at 37 °C.²⁸ With D₂ instead of H₂, extensive deuteration was observed, leading to a mixture of products of both symmetric and unsymmetric D₂ addition (eq 8; for simplicity, the lipid is represented as a general olefin).

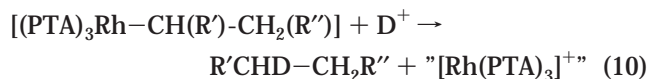


Interestingly, deuterium was also incorporated into the products with H₂ in D₂O solutions but only -CHD- and *no* -CD₂- units were detected by FT-IR spectroscopy (because of the presence of a large number of -CH₂- units in the native lipid, this technique does not distinguish R'CHD-CHDR'', **1**, from R'CHD-CH₂R'' or R'CH₂-CHDR'').

According to ¹H and ³¹P NMR measurements, the reaction of H₂ and [RhCl(PTA)₃] in acidic and neutral aqueous solutions yields stereoisomers of [RhH₂Cl(PTA)₃],^{9b,29} by analogy, we assume the formation of [RhD₂Cl(PTA)₃] under D₂. A concerted transfer of the two D⁻ ligands to the olefin should yield **1**. Formation of unsymmetrically deuterated products, such as **2**, is possible in sequential addition, β-hydride elimination steps (eq 9, [Rh] stands for [RhCl(PTA)₃]).



In D₂O, under H₂, deuteration of the products can take place on two pathways. One involves a fast H-D exchange in [H₂Rh], producing [(D)HRh] and [D₂Rh], and in this case, any of the possible products can be expected in the product mixture. The other possibility is the formation of [HRh(PTA)₃] in a fast dehydrochlorination of [H₂RhCl(PTA)₃]. Incorporation of D could then be the result of deuteriolysis (eq 10) of the Rh-alkyl intermediate obtained by addition of the olefin across the H-Rh bond; in this case, only monodeuteration is expected.



To establish the contribution of the possible pathways, we studied the formation of the various Rh-PTA hydrides, as well as the catalysis of H-D exchange in H₂O by [RhCl(PTA)₃]. It was found that dehydrochlorination of [H₂RhCl(PTA)₃] takes place only in highly basic solutions (pH > 10),²⁹ so [HRh(PTA)₃] is unlikely to play a major role in deuteration of soybean lecithin at pH 4.7. Conversely, in acidic solutions, [RhCl(PTA)₃] was found to be an active

catalyst of the H-D exchange in water³⁰ (with both D₂/H₂O and H₂/D₂O, a turnover frequency of up to 900 h⁻¹ at 70 °C), which seems to favor the deuteration proceeding via an H-D exchange on rhodium. Nevertheless, one should be careful with the conclusions, since the presence of an olefin can substantially influence the processes. In a related system using [{RuCl₂(*m*-TPPMS)₂]₂ + *n m*-TPPMS as catalyst, addition of maleic acid resulted in a complete halt of an otherwise fast H-D exchange in water, and isomerization to fumaric acid became the major reaction.³⁰

Already, in one of the earliest studies on aqueous organometallic catalysis, a slow H/D exchange was observed upon catalysis by ruthenium(II) chloride (TOF = 2 h⁻¹ at 80 °C).³¹ The very high activity of [RhCl(PTA)₃] in the same reaction stresses again that in aqueous organometallic catalysis, water is *not* always *innocuous*; it may also be a reactive medium. This should be kept in mind when designing synthetic reactions in aqueous-organic biphasic systems.

Conclusions

Aqueous-organic biphasic processes offer relatively simple and general solutions to the problem of efficient recycling of soluble catalysts together with easy product isolation. One of the central questions to all biphasic reactions is the solubility and phase distribution of the components of the catalytic system (solvent liquids, substrates, products, gases, catalyst). A unique feature of aqueous-organic two-phase catalysis is in the omnipresence of H⁺ and OH⁻; their actual concentration (i.e., the pH) determines the stability of organometallic catalysts and intermediates in aqueous solution, hence influencing the outcome of the catalytic reaction.

Green Context and Future Directions

The use of aqueous-organic biphasic solvent mixtures for homogeneous catalysis is in line with the fundamental principles of green chemistry. It allows the use of catalytic processes with a mild method of product isolation and catalyst recycling (liquid-liquid phase separation instead of distillation) resulting in fewer byproducts. In cases in which the substrate forms a separate organic phase, the need for an organic solvent can be eliminated. Phase separation contributes to the protection of both the substrates/products and the catalyst against side reactions (degradation), thereby resulting in an increased selectivity. In reactions governed by acid-base equilibria, aqueous-organic biphasic processes allow the fine-tuning of selectivity by proper manipulation of the pH of the aqueous phase.

The past decade has witnessed the rapid expansion of research on liquid biphasic catalysis in various mixtures of organic, fluorinated, supercritical, and ionic liquids. In addition to the possibility of developing two-phase catalytic systems with any of these solvents *and water*, the enormous experience derived from the study of aqueous systems (catalyst modification, reaction kinetics, etc.) will

be of high value in research on any biphasic process. Furthermore, water is still the cheapest and the most abundant and environmentally benign solvent; therefore, aqueous–organic biphasic catalysis will secure for many years its contributions to biphasic applications of transition-metal catalysis in solution.

I am deeply indebted to all my students and co-workers who have contributed to our research on aqueous organometallic catalysis; their names appear in the references. Special thanks are due to Mihály T. Beck, who initiated the study of water-soluble phosphine complexes, and to Zoltán Tóth and Ágnes Kathó for their invaluable contributions in the earlier and later phases of the work, respectively. Part of these studies was done in a fruitful collaboration with Donald J. Darensbourg (Texas A&M University). I highly appreciate the stimulating joint work with László Vigh and Ibolya Horváth (Biological Research Center, Hungarian Academy of Sciences) on the hydrogenation of biomembranes. The continuous support by the National Research Fund (OTKA) of Hungary (research grants) and of Johnson Matthey (JM) Ltd. (precious metal loans) are gratefully acknowledged.

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