<table>
<thead>
<tr>
<th>Title</th>
<th>pH-Dependent isotope exchange and hydrogenation catalysed by water-soluble NiRu complexes as functional models for [NiFe]hydrogenases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Kure, Bunsho; Matsumoto, Takahiro; Ichikawa, Koji; Fukuzumi, Shunichi; Higuchi, Yoshiki; Yagi, Tatsuhiko; Ogo, Seiji</td>
</tr>
<tr>
<td>Citation</td>
<td>Dalton transactions. 35, p. 4747-4755</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2008-09-21</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10297/5207">http://hdl.handle.net/10297/5207</a></td>
</tr>
<tr>
<td>Rights</td>
<td>Copyright © The Royal Society of Chemistry 2008.</td>
</tr>
</tbody>
</table>
pH-Dependent isotope exchange and hydrogenation catalysed by water-soluble NiRu complexes as functional models for [NiFe]hydrogenases†

Bunsho Kurea, Takahiro Matsumotob, Koji Ichikawac, Shunichi Fukuzumid, Yoshiki Higuchied, Tatsuhiko Yagif and Seiji Ogo*a

† Received 6th May 2008, Accepted 16th July 2008
First published as an Advance Article on the web 30th July 2008
DOI: 10.1039/b807555g

The pH-dependent hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes has so far been the subject of controversy. 

Introduction

Hydrogenases (H2ases) are enzymes that catalyse the reversible interconversion of H2 into two protons and two electrons under ambient conditions.1,2 The enzymes also catalyse hydride transfer and electronic reduction of the electron carriers (e.g., NAD+ and cytochrome c) with H2.3–10 H2ases are classified into two major families on the basis of the metal content of their respective dinuclear active sites, i.e., [NiFe]H2ases11–13 and [FeFe]H2ases.14,15 X-Ray analysis, spectroscopic techniques and theoretical methods on the structures of the H2ases have shown that the active sites of both types of H2ases have characteristic bimetallic units with bis(μ-thiolato) ligands, M(μ-SR)2M (M = Ni or Fe, μ-SR)2 = two bridging cysteine residues, 1,3-propanedithiolato or di(thiomethyl)amine, and unidentified ligands (depicted as X in Fig. 1).11–16 The unidentified ligands are proposed to be oxygen ligands such as H2O, OH− or O2− in the resting state, and might be a hydride (H−) ligand in the active state.11,14–16

![Fig. 1 Active site structures of resting forms of [NiFe]H2ases (a) and [FeFe]H2ases (b) (X = H2O, OH− or O2−, Y = CH2 or NH).](image)

Important parts of our understanding of the H2-activation mechanism come from studies on protein film voltammetry,17 and the hydrogen isotope exchange reaction between gaseous isotopes (H2, HD and D2) and medium isotopes (H+ and D+)18–30 catalysed by H2ases (eqn (1)), i.e., H2 bound to the enzyme (E) is split heterolytically to form H+ and an enzyme hydride (EH−) (eqn (2)).18–21 The backward reaction in eqn (2) regenerates H2. In D2O, EH− should react with D+ to provide E with evolution of HD (eqn (3)). In such a case, H2 must be initially converted to HD as a single exchange product and then D2 as a double exchange product in D2O, i.e., the generation of HD and D2 must be sequential.18 However, all experiments of hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes with H2ases performed till now have shown that the single exchange product (HD) and the double exchange products (D2 or H2) were formed simultaneously.18–30 Thus, the detail of the mechanism of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes has so far been the subject of controversy.

![Image](image)

\[ \begin{align*}
    \text{(1)} &
    \text{H}_2 + 2\text{D}^+ &
    \xrightarrow{0 < x < 1}
    \text{xHD} + (1-x)\text{D}_2 + x\text{D}^+ + (2-x)\text{H}^+ \\
    \text{(2)} &
    \text{H}_2 + \text{E} &
    \xrightarrow{}
    \text{H}^+ + \text{EH}^{-} \\
    \text{(3)} &
    \text{D}^+ + \text{EH}^{-} &
    \xrightarrow{}
    \text{HD} + \text{E}
\end{align*} \]
Table 1 Hydrogen isotope exchange reaction between gaseous isotopes (H₂, HD and D₂) and medium isotopes (H⁻ and D⁻) and hydrogenation of substrates catalysed by M(μ-Z)₂M (M = metal ions, Z = thiolato, sulfido or hydrosulfido ligands) complexes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Isotope exchange</th>
<th>Time-dependent generation of isotopes</th>
<th>Hydrogenation</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td></td>
<td>H₂/D⁻</td>
<td>ND'</td>
<td>Ethylene/ethane</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>2*</td>
<td></td>
<td>H₂/D⁻</td>
<td>ND'</td>
<td>Sulfur/hydrogen sulfide/</td>
<td>Chloroform-d₁</td>
</tr>
<tr>
<td>3*</td>
<td></td>
<td>—</td>
<td>—</td>
<td>Cyclohexene/cyclohexane</td>
<td>Toluene</td>
</tr>
<tr>
<td>4*</td>
<td></td>
<td>—</td>
<td>—</td>
<td>1-Octyne/octane, 1-octene and 2-octene</td>
<td>Acetone</td>
</tr>
<tr>
<td>5</td>
<td>This work</td>
<td>H₂/D⁻</td>
<td>—</td>
<td>Benzaldehyde/benzyl alcohol</td>
<td>Water</td>
</tr>
</tbody>
</table>

*Ref. 32–35. *Ref. 36. Ref. 39. *Ref. 40. ND: not determined. /Hydrogenation of β-hydroxystyrene and azobenzene was also reported by similar complexes (ref. 37 and 38).

There are a few studies of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes and hydrogenation of unsaturated compounds catalysed by the M(μ-Z)₂M complexes (Table 1). However, time-dependent hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes has never been carried out with the M(μ-Z)₂M complexes (indicated as ND in Table 1).

All hydrogenation with the M(μ-Z)₂M complexes proceeds in organic solvents but not in water in which the H₂ases operate.

Frontier works on model studies for [NiFe]H₂ases have been carried out by Rauchfuss and co-workers, Artero and Fontecave and co-workers and DuBois and co-workers. We recently reported the synthesis and structures of water-soluble [Ni(μ-SR)₂Ru(μ-OH)(η⁶-C₆Me₆)](OTf)₂ ([1](OTf)₂, (μ-SR)₂ = N,N'-dimethyl-N,N'-bis(2-mercaptoethyl)-1,3-propanediamine, OTf = CF₃SO₃ and [Ni(μ-OH)(μ-SR)₂(μ-H)Ru(η⁶-C₆Me₆)](NO₃) (2)](NO₃) as functional models for the resting form (E) and the active form (EH⁻) of [NiFe]H₂ases, respectively (Fig. 2).

The structures of 1 and 2 were determined by X-ray and neutron diffraction analyses.

We report herein the pH-dependent hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes at pH 4–6 catalysed by 2 via a low-valent intermediate [Ni(μ-SR)₂Ru(η⁶-C₆Me₆)] (3), and hydrogenation of the carbonyl compounds at pH 7–10 catalysed by [Ni(μ-OH)(μ-SR)₂(μ-H)Ru(η⁶-C₆Me₆)] (4), which is a deprotonated species of 2 whose pKₐ value is 6.5 (Fig. 3).
Experimental

Materials and methods

\[ \text{[Ni}^{II} \text{(μ-SR)}_{2} \text{Ru}^{II} \text{(OH)}_{2} \text{(η}^{6-}\text{C}_{6}\text{Me}_{6}) \text{]} \text{(OTF)}_{2} \text{]} \text{[I}(\text{OTF)}_{2}, \text{ (μ-SR)}_{2} \text{]} \]

Propanedithiol, OTF = CF_{3}SO_{3} was prepared by the method described in the literature.\textsuperscript{5}[Ni^{II}(\text{OH})_{2}(\text{μ-SR})_{2}(\text{μ-H})\text{Ru}^{II}(\text{η}^{6-}\text{C}_{6}\text{Me}_{6})]([NO}_{3})_{2}([2](\text{NO}_{3})) was synthesised from the reaction of 1 with H_{2} (0.1 MPa) in the range of pH 4–7 at 25 °C.\textsuperscript{53} The manipulations in the acidic media were carried out with plastic- and glass-ware (without metals). Distilled water, 0.1 M NaOH/H_{2}O and 0.1 M HNO_{3}/H_{2}O were purchased from Wako Pure Chemical Industries, Ltd., 65% DNO_{3}/D_{2}O (99% D) was purchased from Isotec Inc., K_{2}DPO_{4} (99% D) was purchased from Sumitomo Seik a Chemicals Co., Ltd., and HD_{20} Wako Pure Chemical Industries, Ltd., 65% DNO_{3}/D_{2}O (99% D) was purchased from Isotec Inc., K_{2}DPO_{4} (99% D) was purchased from Aldrich Co., and D_{2}O (99.9% D), 40% NaOD/D_{2}O (99% D) and KD_{2}PO_{4} (98% D) were purchased from Cambridge Isotope Laboratories, Inc.; these were used without further purification.

Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF-MS) was recorded on a VGT ultraflex TOFTOF (Bruker Daltonics), where dithanolamine was used as a matrix. Electroless ionisation mass spectrometry (EIS-MS) data were obtained by an API 365 triple-quadrupole mass spectrometer (PE-Sciex) in the positive detection mode, equipped with an ion spray interface. The sprayer was held at a potential of +5.0 kV, and compressed N_{2} was employed to assist liquid nebulisation. 1H NMR spectra were recorded on a JEOL JNM-AL300 spectrometer at 23 °C. H_{2}, HD and D_{2} gases were used as received. H_{2} gas (99.9999%) was purchased from Taiyo Toyo Sanso Co., Ltd., D_{2} gas (99.5%) was purchased from Sumitomo Seika Chemicals Co., Ltd., and HD gas (HD 97%, H_{2} 1.8%, D_{2} 1.2%) was purchased from Isotec Inc.; these were used without further purification.

The pH of the solution was adjusted by using 0.1 M HNO_{3}/H_{2}O (pH 1–3), 25 mM CH_{3}COOH/CH_{3}COONa (pH 4–6), 25 mM NaHPO_{4}/KH_{2}PO_{4} (pH 7–8) and 0.1 M NaOH/H_{2}O and 0.1 M HNO_{3}/H_{2}O were purchased from Wako Pure Chemical Industries, Ltd., 65% DNO_{3}/D_{2}O (99% D) was purchased from Isotec Inc., K_{2}DPO_{4} (99% D) was purchased from Aldrich Co., and D_{2}O (99.9% D) was purchased from Sumitomo Seik a Chemicals Co., Ltd., and HD gas (HD 97%, H_{2} 1.8%, D_{2} 1.2%) was purchased from Isotec Inc.; these were used without further purification.

The pH value of the aqueous phase is adopted.

\[ \text{pH} \text{value of the aqueous phase is adopted.} \]

\[ 6), 25 \text{mM NaHPO}_{4}/\text{KH}_{2}\text{PO}_{4} (\text{pH 7–8}) \text{ and 0.1 M NaOH/H}_{2}\text{O} \]

Values were corrected by adding 0.4 to the observed values (pD = pH meter reading + 0.4).\textsuperscript{56,57} In the biphasic media, the pH value of the aqueous phase is adopted.
in the sample could be derived from the NaOH/H2O solution used for adjusting the pH of the solution and the counteranion of [2](NO3), respectively. The existence of NO3 was confirmed by IR measurement, i.e., a characteristic absorption of uncoordinating NO3 was observed at 1384 cm⁻¹. ESI-MS (in CH3CN m/z 543.2 (4–OH); I = 100% in the range m/z 100–2000). FTIR (cm⁻¹, as a KBr disk); 3433 (O–H), 1743 (Ni–H–Ru), 1570 (aromatic C–C), 1473 (aromatic C–C), 1465 (aromatic C=C), 1384 (NO3–), 1328, 1290, 1262, 1207, 1110, 1097, 1067, 1044, 1025, 972, 951, 803. XPS: 853.9 eV (Ni 2p3/2 region), 280.5 eV (Ru 3d5/2 region).

Typical procedure for hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes catalysed by [2](NO3)

A 3 mL vial was charged with 1.0 μmol of [2](NO3) and a stir bar under H2, and was capped with a septum. After injecting 1 mL of Ar-bubbled D2O into the vial, 1 mL of H2 gas was removed immediately. The vial was stirred (5000 rpm, Nissin magnetic stirrer Model SW-R700) vigorously at 60 °C for 1 h. The gas present in the vial was sampled using a gas-tight syringe and analysed for H2, HD and D2 gases by GC. Isotope ratios for each of the identical runs were averaged. It was confirmed that no isotope exchange reactions between gaseous isotopes and medium isotopes occurred in the absence of 1, 2 or 3 (as blank experiments). When the experiments were performed using D2 and H2O, the results were the same except for the isotope effects, and the H2/HD ratio was comparable to the D2/HD ratio of the H2/D⁻ isotope exchange reaction.

Typical procedure for the hydrogenation of carbonyl compounds catalysed by 4

Benzaldehyde (250 mmol) and 4 (3.1 mg, 5.0 μmol) were dissolved in H2O (2 mL) at pH 7–10. After injecting 1 mL of Ar-bubbled D2O into the vial, 1 mL of H2 gas was removed immediately. The vial was stirred (5000 rpm, Nissin magnetic stirrer Model SW-R700) vigorously at 60 °C for 1 h. The solution was cooled to 0 °C, and the resulting mixture was extracted by CDCl3. The yield of benzyl alcohol in the CDCl3 solution was determined by 1H NMR with 1,4-dioxane as an internal standard. It was confirmed that no hydrogenation occurred in the absence of 1 or 4 (as blank experiments).

Results and discussion

Behavior of Ni(µ-H)Ru complexes in acidic media (at pH 4–6)

Only crystals of 2 [Ni(µ-H)Ru] and the D-labeled 2 [Ni(µ-D)Ru] available for X-ray analysis were used for all experiments in this study. It is very important to note that the hydride complex 2 does not react with H2 to evolve H2 in acidic media at pH 4–6, i.e., complex 2 does not decompose to the aqua complex 1 with the evolution of H2 in acidic media at pH 4–6. It was confirmed by ESI-MS (Fig. S1 in ESI†) and IR (Fig. S2 in ESI†) that the structure of 2 was preserved in acidic media at pH 4–6. The hydrido ligand of 2 exhibits a protic character and undergoes an H²/D⁻ exchange with D⁻ in D2O at pD 4–6 (eqn (4)).

Fig. 4 pD-Dependent H⁺/D⁺ exchange of the hydrido ligand of [2](NO3) (1.0 μmol) in D2O (1 mL) at pD 1–10 at 60 °C for 15 min.

A low-valent complex Ni(µ-SR)2RuI

Complex [2](NO3) was dissolved in H2O at pH 4–6. H2 gas was bubbled through the solution at 23 °C, to evaporate the solvent, for 1 h. The remaining red oil was extracted with chloroform and the resulting solution was filtered and evaporated under vacuum to yield a dark red powder of 3. It is important to note that the low-valent complex 3 was not obtained from the reaction of 2 with H2 in neutral–basic media at pH 7–10. Fig. 5a shows a MALDI-TOF mass spectrum of a signal at m/z 542.1 [relative intensity (I) = 100% in the range m/z 200–1000]. The envelope at m/z 542.1 has a characteristic distribution of isotopomers that matches well with the calculated isotopic distribution for [3]⁺ (Fig. 5b and 5c). X-ray photoelectron spectra (XPS) of 3 show that the binding energies of Ni 2p3/2 and Ru 3d5/2 are 852.7 eV and 279.4 eV, which correspond to Ni(I) and Ru(I), respectively (Fig. 6). The values of the binding energies of Ni 2p3/2 and Ru 3d5/2 in 3 are lower than those of [1](NO3)2 (Ni 2p3/2: 853.9 eV, Ru 3d5/2: 280.3 eV). 1H NMR measurement indicates diamagnetism in 3, i.e., the signals of the protons of η6-C6Me6 and (µ-SR)2 of 3 were observed at 2.12 and 1.80–1.92 ppm, respectively. The reason for diamagnetism should be explained on the basis of electronic coupling between the two metal ions (NiI and RuI).
Fig. 5 (a) MALDI-TOF mass spectrum of 3. Dithranol was used as a matrix. The signal at m/z 542.1 corresponds to \([3]\)•+. (b) The signal at m/z 542.1. (c) Calculated isotopic distribution for \([3]\)•+.

Fig. 6 (a) XPS of Ni 2p region for 3. (b) XPS of Ru 3d region for 3.

Hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes catalysed by the D-labeled 2 in acidic media (at pH 4–6)

The D-labeled 2 catalyses a pD-dependent hydrogen isotope exchange reaction between H\(_2\) and D\(_2\)O as shown in Fig. 7. The pD-dependence of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes (Fig. 7) is similar to the pD-dependence in the H\(^+\)/D\(^+\) exchange (Fig. 4). The evolution of HD and D\(_2\) was determined by GC.

Fig. 7 pD-Dependent generation of HD and D\(_2\) in the reaction of \([2](NO_3^-)\) (1.0 \(\mu\)mol) with H\(_2\) (2.0 cm\(^3\), 84 \(\mu\)mol, 0.1 MPa) in D\(_2\)O (1 mL) at 60 °C for 1 h.

The time course of the hydrogen isotope exchange reaction between H\(_2\) and D\(_2\)O (or between D\(_2\) and H\(_2\)O) catalysed by the D-labeled 2 (or 2) shows that HD and D\(_2\) (or HD and H\(_2\)) are formed simultaneously as shown in Fig. 8a (or Fig. 8b), which agrees with the time-dependent profile in the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes by H\(_2\)ases.\(^{18–30}\) The data of the consumption of H\(_2\) (Fig. 8a) and D\(_2\) (Fig. 8b) were used for the first-order kinetic plots in Fig. 8c. The consumption of H\(_2\) (or D\(_2\)) obeyed the first-order kinetics over 3–5 half-lives. In this case, a kinetic isotope effect (KIE = 1.7, \(k_{\text{H}}/k_{\text{D}} = 1.03 \times 10^{-4} \text{ s}^{-1}\) and \(k_{\text{H}}/k_{\text{D}} = 6.11 \times 10^{-5} \text{ s}^{-1}\)) was observed (Fig. 8c). The presence of the KIE is consistent with a mechanism in which the rate-determining step involves H–H (or D–D) bond cleavage.

Fig. 8 (a) Time course of the generation of HD and D\(_2\) and the consumption of H\(_2\) determined by GC analysis in the reaction of \([D\text{-labeled}]2(\text{NO}_3^-)\) (1.0 \(\mu\)mol) with H\(_2\) (2.0 cm\(^3\), 84 \(\mu\)mol, 0.1 MPa) in D\(_2\)O (1 mL, pD 4.0) at 60 °C. (b) Time course of the generation of HD and H\(_2\) and the consumption of D\(_2\) determined by GC analysis in the reaction of \([2](\text{NO}_3^-)\) (1.0 \(\mu\)mol) with D\(_2\) (2.0 cm\(^3\), 84 \(\mu\)mol, 0.1 MPa) in H\(_2\)O (1 mL, pH 4.0) at 60 °C. (c) The first-order kinetic plots for the consumption of H\(_2\) (Fig. 8a) and D\(_2\) (Fig. 8b).

The pH-dependence and time course of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes catalysed by 1 and 2 are similar to those catalysed by the D-labeled 2.

Mechanism of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes in acidic media

Based on the results obtained, we propose a mechanism of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes. In Fig. 9, D-labeled 2 is used as a
starting complex whose $\mu$-D ligand has a D$^+$ character, but not a D$^-$ character at pD 4–6 (vide supra). First, the reaction of the D-labeled 2 with H$_2$ may produce a single D-labeled dihydride species Q (HD hydride) via heterolytic activation of H$_2$. This may be a rate-determining step for the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes judging from the observed KIE as shown in Fig. 8c. The H$^+$/$\text{D}^+$ exchange of Q with D$^+$ in D$_2$O occurs quickly to give a double D-labeled dihydride species R (DD hydride). Then, intramolecular reductive elimination of HD from Q and D$_2$ from R occurs to give the low-valent complex 3. This is the reason why HD and D$_2$ are produced simultaneously (but not sequentially). To complete the catalytic cycle, the D-labeled 2 is regenerated by deuteration of 3. This is totally different from the previously proposed mechanism of the hydrogen isotope exchange reactions between gaseous isotopes (H$_2$) and medium isotopes (D$_2$O), where the hydrido ligand of the metal hydride species (M–H) acts as H$^-$ and reacts with medium D$^+$ to form HD as the first step in the reaction.$^{43,47,49}$ It was confirmed that the low-valent complex 3 also catalysed the hydrogen isotope exchange reaction between H$_2$ and D$_2$O (or between D$_2$ and H$_2$O).

Behavior of Ni(\(\mu\)-H)Ru complexes in neutral-basic media (at pH 7–10)

Complex 2 is reversibly deprotonated to form 4, which is a deprotonated species of 2, in neutral–basic media at pH 7–10 (eqn (5)).$^{60}$

$^5$ UV-vis titration experiments revealed that the p$K_a$ value of 2 was 6.5 (Fig. 10). It is well known that aqua complexes can deprotonate to form hydroxo complexes in neutral–basic media.$^{61-65}$ $^1$H NMR measurements indicate paramagnetism in 4 (Fig. S3 in ESI†). A similar character was observed in 2.$^{53}$

In an IR spectrum of 4 in the 650–4000 cm$^{-1}$ region as a KBr disk, a peak at 3433 cm$^{-1}$ was assigned to $\nu$(O–H) that shifts to 2688 cm$^{-1}$ by isotopic substitution of a hydrogen atom in the hydroxo ligand (OD),$^{66}$ although the O–H stretching observed by IR is not direct evidence for the existence of 4.$^{67}$

Fig. 9 A proposed mechanism of the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes. D-Labeled 2 is used as a starting complex with H$_2$ in D$_2$O at pD 4–6.

Fig. 10 pH-Dependent UV-vis spectra of 2 (4.7 $\times$ 10$^{-5}$ M) in the pH range 4.5–9.5. The inset gives a plot of absorbance (\(\lambda\) = 296 nm) versus pH. Experiments were performed by the titration of 2 with 0.1 M NaOH/H$_2$O at 23 °C.

Stoichiometric hydrogenation of carbonyl compounds with 4 in neutral-basic media at pH 7–10 (without H$_2$)

Complex 4 has a reducing ability toward carbonyl compounds such as benzaldehyde at pH 7–10 under stoichiometric conditions (4 : carbonyl compound = 1 : 1) in the absence of H$_2$ (eqn (6)), e.g., benzaldehyde is reduced to benzyl alcohol (yield: 6%) with 4 at pH 8 at 60 °C for 1 h.

Fig. 11 shows the pH-dependent yield (based on 4) of the $\alpha$-fluorobenzyl alcohol that was obtained by a reaction of 4 with $\alpha$-fluorobenzaldehyde under N$_2$ in the absence of H$_2$ at 60 °C for 15 min, i.e., the reduction takes place in the neutral–basic media at pH 7–10.

Fig. 11 pH-Dependent yield (based on 4) of the $\alpha$-fluorobenzyl alcohol that was obtained by a reaction of 4 with $\alpha$-fluorobenzaldehyde under N$_2$ in the absence of H$_2$ at 60 °C for 15 min under N$_2$ in the absence of H$_2$. 
Catalytic hydrogenation of carbonyl compounds with 4 in neutral–basic media at pH 7–10 (with H₂)

On the other hand, under catalytic conditions (0.5 MPa of H₂), benzaldehyde (50 equivalents) is reduced to benzyl alcohol catalysed by 4 in H₂O at pH 8 at 60 °C for 12 h (yield: 98%, eqn (7)).

(7)

To the best of our knowledge, this is the first example of the hydrogenation of substrates catalysed by M(μ-Z)₂M (M = metal ions, Z = thiolato, sulfido or hydrosulfido ligands) complexes in aqueous media. ¹H NMR experiments revealed that the D-labeled hydrogen atoms were incorporated into the carbonyl compounds when D₂ was used as the hydrogen donor in the hydrogenation (eqn (8)).

(8)

The pH-dependence on the catalytic reduction of glyoxylic acid under H₂ (0.5 MPa) is similar to the pH-dependence on the reduction under the stoichiometric conditions described above (Fig. S4 in ESI†).

Fig. 12 reveals temperature-dependent turnover frequencies {TOFs = (mol of product formed/mol of catalyst) per h} in the hydrogenation of o-fluorobenzaldehyde catalysed by 4 in H₂O at pH 8 at 0.5 MPa of H₂. The TOFs of the hydrogenation were drastically increased above 40 °C. The catalytic reactions were carried out at 60 °C, and it was confirmed by ESI-MS that complex 4 was quite stable at 60 °C under Ar at pH 7–10 in the absence of reducible aldehydes. Fig. 13 shows the dependence of TOFs upon concentrations of o-fluorobenzaldehyde used in the hydrogenation catalysed by 4 in H₂O at pH 8 at 60 °C. The TOFs of the hydrogenation of aldehydes examined in this study saturate at a 1 : 50 ratio of 4 : aldehydes. As shown in Fig. 14, the TOFs of the hydrogenation of o-fluorobenzaldehyde catalysed by 4 in H₂O at pH 8 at 60 °C are dependent on the pressure of H₂ in the range from 0.1 to 0.5 MPa, and saturate at 0.5 MPa. Fig. 15 shows the time course of the turnover numbers (= TONs, mol of product formed/mol of catalyst) in the hydrogenation of o-fluorobenzaldehyde under the optimised catalytic conditions (pH 8, 60 °C, 0.5 MPa of H₂, 1 : 50 ratio of 4 : aldehydes). In addition, it was confirmed that the catalyst 4 could be reused at least three times; i.e., upon addition of more substrates after the reaction, the catalytic cycle was resumed (Fig. 16), though the catalyst 4 was gradually deactivated.
Fig. 16 Resumption of the catalytic hydrogenation of o-fluorobenzaldehyde (250 μmol) with 4 (5 μmol) in H2O (2 mL) at 60 °C at 0.5 MPa of H2.

Table 2 summarises the hydrogenation of aldehydes catalysed by 4 under the optimised catalytic conditions. The water-soluble aldehyde (glyoxylic acid) is converted to the corresponding alcohol much more efficiently than water-insoluble aldehydes (benzaldehyde and o-fluorobenzaldehyde). The TOF of the hydrogenation of a benzaldehyde derivative containing an electron-withdrawing group (o-fluorobenzaldehyde) is higher than the TOF of the hydrogenation of benzaldehyde at pH 8 at 60 °C.

Table 2 Hydrogenation of water-soluble aldehydes (entries 1 and 2) in water and water-insoluble aldehydes (entries 3 and 4) in biphasic media catalysed by 4 at pH 8°

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>TOF°</th>
<th>t/h</th>
<th>Yield (%)</th>
<th>T/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HOCOHH</td>
<td>HOCOHO</td>
<td>3</td>
<td>24</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>HOCOHH</td>
<td>HOCOHO</td>
<td>24</td>
<td>4</td>
<td>98</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>HOCOHH</td>
<td>HOCOHO</td>
<td>6</td>
<td>12</td>
<td>98</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>HOCOHH</td>
<td>HOCOHO</td>
<td>11</td>
<td>9</td>
<td>99</td>
<td>60</td>
</tr>
</tbody>
</table>

* In the case of biphasic media (entries 3 and 4), the pH value of the aqueous phase is adopted. ° Turnover frequency: (mol of product formed/mol of 4) per h.

Mechanism of the catalytic hydrogenation of carbonyl compounds

The catalytic cycle of the hydrogenation of the water-soluble and water-insoluble aldehydes catalysed by 4 is shown in Fig. 17. The hydride complex 4 reacts with aldehydes to afford the corresponding alcohols and the aqua complex 1. Complex 4 is regenerated by the reaction of the aqua complex 1 with H2 at pH 7–10. It is known that the H2O ligand accelerates the heterolytic H2-activation in polar solvents to release H3O+.68–70

Fig. 17 A proposed mechanism of the hydrogenation of the carbonyl compounds in H2O at pH 7–10.

Conclusions

We have succeeded in the pH-dependent hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes catalysed by 2 at pH 4–6 and hydrogenation of carbonyl compounds catalysed by 4 at pH 7–10. In the hydrogen isotope exchange reaction between gaseous isotopes and medium isotopes, the generation of HD and D2 (or HD and H2) is simultaneous and pH-dependent, which is similar to H2ases. A low-valent NiI(μ-SR)2RuI complex 3 has been isolated by the reaction of 2 with H2 in acidic media at pH 4–6. The formation of 3 by reductive elimination of HD and D2 (or HD and H2) from the dihydride species produced by the reaction of 2 with H2 (or D2) is the key step for the simultaneous generation of HD and D2 (or HD and H2). In the hydrogenation, complex 4 can reduce the aldehydes to the corresponding alcohols in H2O. Thus, the μ-H ligand of the NiII(μ-SR)2(μ-H)RuII complexes has both protic character (at pH 4–6) and hydridic character (at pH 7–10) depending on pH.

Acknowledgements

This work was supported by a grant in aids: 17350027, 17655027, 18030401, and 18065017 (Chemistry of Concerto Catalysis), and the Global COE Program, “Science for Future Molecular Systems” from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references
