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Mechanism of formation of active catalytic species in nickel-catalysed asymmetric hydrogenation

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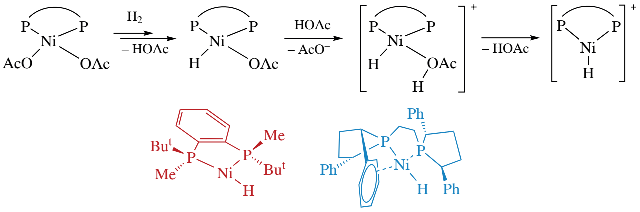
Initial stages of two representative Ni-catalysed asymmetric hydrogenations were investigated computationally featuring the formation of the active catalytic species [*R*,*R*-BenzP*NiH]$^+$ from *R*,*R*-BenzP*Ni(OAc)$_2$ and [*S*,*S*-Ph-BPENiH]$^+$ from *S*,*S*-Ph-BPENi(OAc)$_2$. Among several computed pathways the most feasible is dissociation of acetic acid from (ligand)NiH(HOAc) formed by H_2 metathesis in the (ligand)Ni(H_2)(OAc)$_2$. The rate-limiting step is the initial metathesis of H_2 requiring high effective activation barriers of 28.3 and 26.6 kcal mol^{-1}, in accord with high pressures and elevated temperatures essential for the Ni-catalysed hydrogenations.



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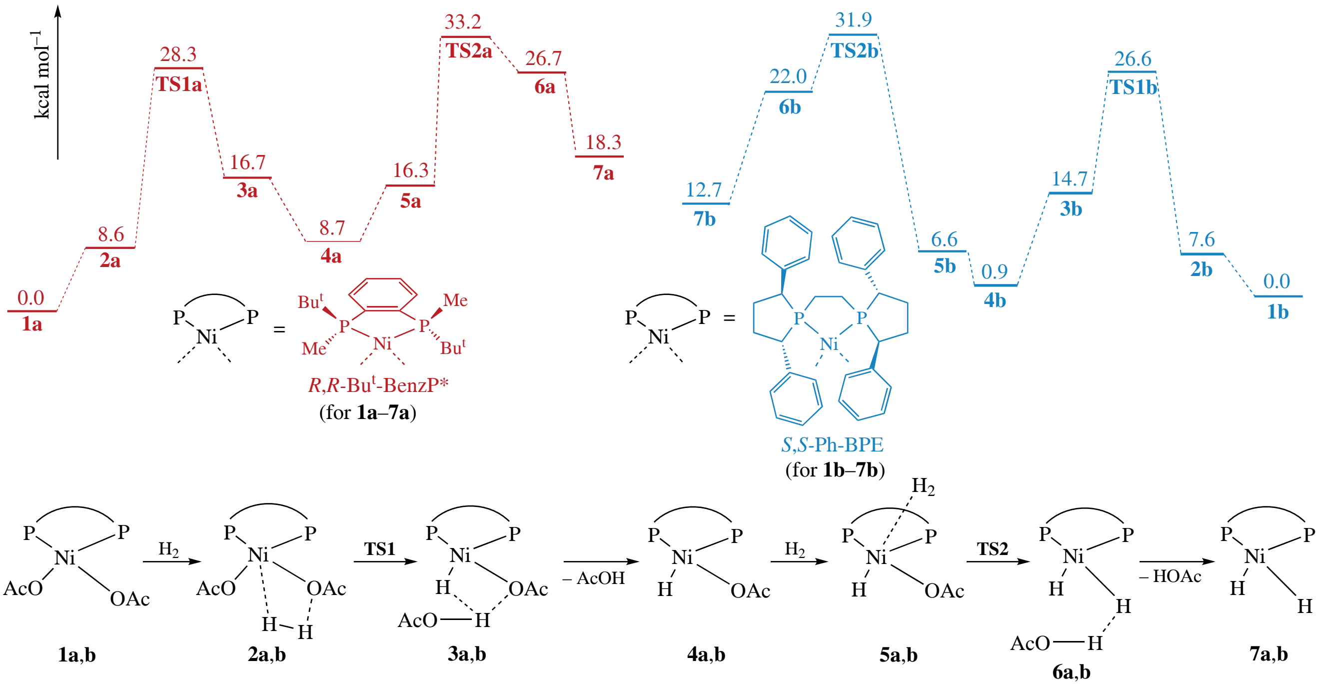
Transition metal catalysed asymmetric hydrogenation has become a powerful method for creation of chiral compounds that can be further used for design and synthesis of chiral drugs and new candidates for various applications requiring enantiomerically pure compounds.[1,2] Historically the method was developed based on the application of chiral complexes of noble metals such as Rh,[3–7] Ru,[8–10] Ir[11,12] and Pd.[13,14] Although new reactions applying noble metals continue to appear, the modern trend shifted to wider use of the complexes of earth abundant (and accordingly much cheaper) metals like Fe,[15,16] Ni,[17,18] Co,[19–21] Mn[22] or Cu.[23] Additional bonus making the use of these metals is their relative environmental benignity.

It is a common knowledge that in such a sophisticated technology like asymmetric hydrogenation, understanding of the reaction mechanisms including the details of the catalytic cycles is essential for successful development of new effective catalysts and proper adjustment of the reaction conditions. Following successful developments in this field for Ru, Rh, Ir and Pd catalysts, important mechanistic results were recently published for asymmetric hydrogenation using Co (propene[24] and enamide[25]), Ni (variously substituted C=N bonds),[26–28] Mn (acetophenone, heterocycles),[28–31] Cu (conjugated pentenones)[32] catalysts. However, further research in this area is strongly wanted.

In particular, the structure of the active catalytic species is relatively elusive compared to the noble metal catalysed asymmetric hydrogenations due to greater number of possibilies, involvement of paramagnetic species and other technical difficulties. Since the publication of experimental and computational studies of the Pd case identifying a [P_2Pd–H]$^+$ complex as the most probable catalyst in the asymmetric hydrogenation, it has been (not unreasonably) assumed that similar species could play the same role in earth abundant metals catalysed hydrogenations. More recently published computational study of the early stages of the Co-catalysed asymmetric hydrogenations confirmed the early assumptions.[33]

In this work we investigate the mechanism of generation of the active catalytic species in Ni-catalysed asymmetric hydrogenation (for computational methods, see Online Supplementary Materials). The Ni complexes of *R*,*R*-Bu^t-BenzP* and *S*,*S*-Ph-BPE (Scheme 1) were chosen for this study since the corresponding catalytic cycles and the mechanisms of enantioselection were recently published.[27,28]

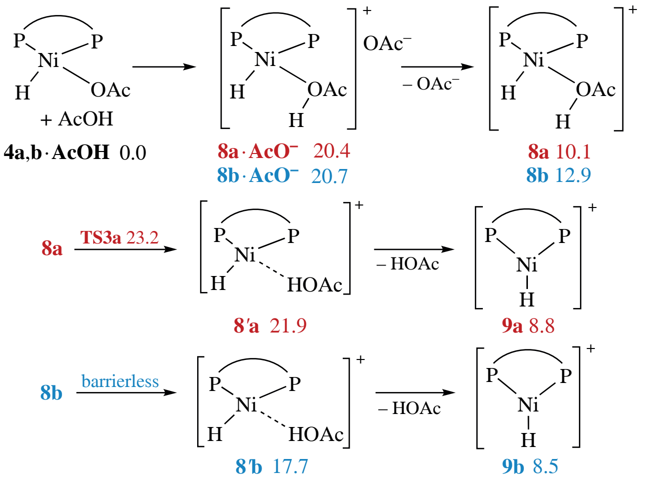
Unlike the reactions catalysed by chiral complexes of noble metals, Ni is often introduced to the system in a form of hydrated salt, *e.g.* Ni(OAc)$_2\cdot 4H_2O$ accompanied with equimolar amount of the ligand. Therefore, we started our analysis from the chelate complexes which can easily form under these conditions (see Scheme 1). These complexes react with dihydrogen yielding adducts of **1a**,**b** with H_2. Metathesis of dihydrogen proceeds through the **TS1a**,**b** and after dissociation of the weakly bound in **3a**,**b** acetic acid, leads to the Ni hydrides **4a**,**b**. This is the rate-limiting step of the initial stage of the reaction with computed effective Gibbs free activation energies of 28.3 and 26.6 kcal mol^{-1}, respectively (see Scheme 1). Metathesis of another molecule of dihydrogen through **TS2a**,**b** followed by dissociation of acetic acid yields neutral Ni dihydrides **7a**,**b**. However, the latter species are unlikely intermediates in the real catalytic cycles, because the **TS2a**,**b** are significantly higher in energy than the **TS1a**,**b**, and the formation of **7a**,**b** is strongly endergonic. We also considered a possibility of the generation of cationic species from the relatively stable neutral hydride complexes **4a**,**b** *via* dissociation of the acetate anion. However, these pathways were computed to be unreasonably high in energy.



Scheme 1 Computed Gibbs free energy profiles for the transformation of the nickel(II) diacetate complexes **1a**,**b** to nickel(II) dihydride complexes **7a**,**b**.

Therefore, we decided to check if protonation of **4a**,**b** could open the door for generation of cationic Ni species. As can be seen from Scheme 1, acetic acid can be formed in the reaction mixture. Moreover, it has been found that addition of acid (either added or formed during hydrogenation) is essential for the smooth hydrogenation of oximes catalysed by the *S*,*S*-Ph-BPE Ni complex.[26]

The computed pathways resulting in the formation of cationic Ni complexes **9a**,**b** are shown in Scheme 2. Protonation of **4a**,**b** yields cationic complexes **8a**,**b**. Then elimination of acetic acid *via* **TS3a** yields the active catalyst **9a**. In the case of the **8b** the same reaction proceeds barrierlessly yielding complex **8′b** stabilized by η^3 coordination of one of the phenyl groups of the *S*,*S*-Ph-BPE ligand (Figure 1). Elimination of acetic acid from **8′b** provides **9b**. Interestingly, these computations predict a milder formation of **9b** compared to **9a** (see Scheme 2). The hydride in **9b** is more effectively stabilized *via* intramolecular CH/π contacts that makes it 4.4 kcal mol^{-1} more stable compared to **8b**. On the other hand, **9a** is only 1.3 kcal mol^{-1} more stable than **8a**. This may be a reason for better performance of the *S*,*S*-Ph-BPE Ni complex compared to the *R*,*R*-Bu^t-BenzP* Ni complex in the asymmetric hydrogenation of oximes.[26]



Scheme 2 Possible pathways leading to the formation of **9a**,**b**. The values standing near the codes are in kcal mol^{-1}.

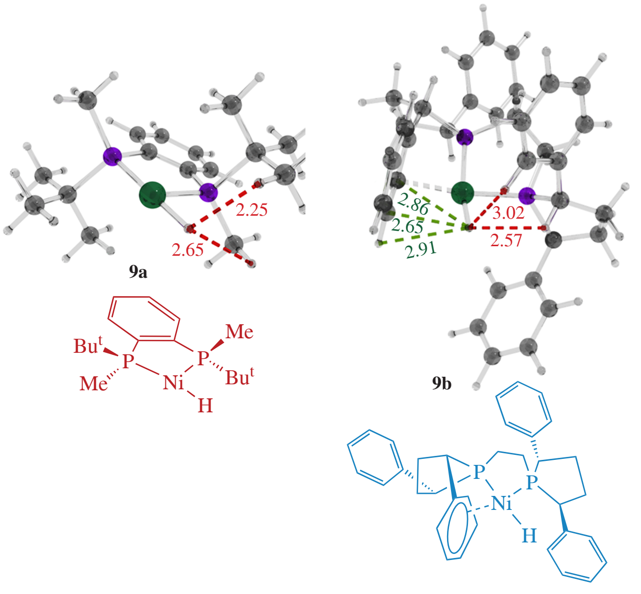


Figure 1 Optimized structures of the active catalysts **9a** and **9b**.

In conclusion, cationic nickel(II) monohydride complexes **9a**,**b**, the true catalysts in the Ni-catalysed asymmetric hydrogenations, can be generated *via* the protonation of acetate complexes **4a**,**b**. The rate-limiting step for the catalyst generation is the metathesis of dihydrogen in a (ligand)Ni(H_2)(OAc)$_2$ molecule. Computational results are in accordance with the experimentally observed higher reactivity of the *S*,*S*-Ph-BPE Ni complex compared to the *R*,*R*-Bu^t-BenzP* Ni complex in the asymmetric hydrogenation of acetophenone oxime.[26]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7818.

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