LiAlH$_4$-catalyzed Imine Hydrogenation with Dihydrogen: New DFT Mechanistic Insights

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Recently, it was found that the widely used stoichiometric reducing reagent LiAlH$_4$ can also be used as a useful catalyst for imine hydrogenation with H$_2$ under relatively mild conditions. In this work, extensive state-of-the-art DFT calculations are conducted to explore the detailed catalytic mechanism. In sharp contrast to the recent proposal involving heterolytic H$_2$ activation over Al–N amide bonds after multiple imine insertion, our new mechanism highlights the dual role of the Lewis-acidic lithium cation in frustrated-Lewis-pair-like activation of both imine substrate and H$_2$ when combined with the aluminum-bound hydride and amide ligands, respectively. Ionic Li–N amide bonds are about 13 kcal/mol more reactive than Al–N amide bonds for H$_2$ activation, thus providing a useful structural feature for rational design of active hydrogenation catalysts.

Since its first discovery in 1947,[1] lithium aluminum hydride (LiAlH$_4$) has been widely used as a highly useful reducing reagent in stoichiometric conversions of polar unsaturated substrates such as ketones and imines into saturated species despite its poor atom efficiency as hydride donor.[2] However, using stoichiometric quantities of LiAlH$_4$ may lead to large amounts of Li/Al salt waste that often complicate product work-up and even have a negative environmental impact. Hence, the catalytic hydrogenation using dihydrogen (H$_2$) as a clean and widely accessible reducing reagent is highly desirable. Catalytic imine hydrogenation with H$_2$ are mostly based on late transition metals (Rh, Ir)[3] that are expensive and highly toxic, with only few exceptions based on sustainable (inexpensive and biocompatible) metal catalysts (Ti, La, Zn, Ni, Cu).[4] Metal-free frustrated Lewis pairs (FLPs)[5] may operate under mild conditions for imine hydrogenation,[6] while bulky imines as Lewis base can be reduced by B(C$_6$F$_5$)$_3$ as Lewis acid catalyst.[7]

Recently, simple main-group metal alanates MAIH$_4$ (M=Li, Na,[8] K)[9] and Al(AlH$_4$)$_2$ (Al=Mg, Ca, Sr)[10] as well as alkaline earth metal amides Aem[Ni(SiMe$_3$)$_2$]$_2$ (Ae=Al, Mg, Ca, Sr, Ba)[11] were also found to be efficient imine hydrogenation catalysts under surprisingly mild conditions (1–6 bar H$_2$, ~80 °C). However, the catalytic reactivity was found in quite different trends with respect to the increasing size of metal cation, which decreases for alkaline (group 1) metals (Li > Na > K)[9] but increases for alkaline earth (group 2) metals (Mg < Ca < Sr).[5]

Based on combined experimental and computational evidences on the LiAlH$_4$-catalyzed hydrogenation of typical imine PhCH=NBu,[9] the experimentally observed amide complex LiAlH$_4$[N$_2$]$_2$ (with [N$_2$] = N(Bu)CH=Ph) was proposed as the actual catalyst generated in situ from double imine insertion of LiAlH$_4$ followed by further imine insertion (forming LiAlH$_4$[N$_2$]$_2$) and rate-limiting H$_2$ addition to the Al–N amide bond to complete the catalytic cycle (Scheme 1, top). However, the computed free energy barrier of ~37 kcal/mol (or enthalpy barrier of 29.2 kcal/mol)[9] for the rate-limiting step seems to be

![Scheme 1. DFT-computed mechanisms of LiAlH$_4$-catalyzed hydrogenation of imine PhCH=NBu with H$_2$ in solution: (top) recent proposal by Harder et al; (bottom) this extensive DFT mechanistic work.](image)
to high to account for the observed mild reactions conditions, thus putting some doubt on the proposed catalytic mechanism.

To gain more general mechanistic insight into the LiAlH₄-catalyzed imine hydrogenation with H₂, extensive state-of-the-art dispersion-corrected DFT calculations at the PW6B95-D3 + COSMO-RS/TPSS-D3 + COSMO level in implicit THF solution (see below for computational details) are conducted using the typical imine substrate PhCH=NtBu (Im). The inclusion of COSMO solvation in geometry optimization is essential to identify potential ionic reactions (such as the formation of separated ion pairs) that are highly disfavored in the gas-phase. In this work, multiple imine insertion and H₂ addition reaction steps are examined in order to identify the true catalytic species in solution. In contrast to recent dispersion-uncorrected DFT calculations based on gas-phase structures, a rather different catalytic mechanism is found in our better DFT calculations including well-defined and chemically reasonable intermediates and novel H₂ activation steps (Scheme 1, bottom).

Our DFT calculations clearly show that a doubly-bridged Li/Al complex is preferred in solution when the Lewis-acidic Li center is coordinatated by imine PhCH=NtBu, but separated ions including Li(THF)⁺ are more stable by about 4 kcal/mol due to a higher affinity of THF to the lithium cation. Even more importantly, bridging Li–N amide bonds are shown to be much more reactive than Al–N amide bonds for H₂ activation, with decreasing reactivity with increasing steric hindrance due to multiple imine insertion. Such mechanistic insights can be useful for rational design of efficient hydrogenation catalysts.

As shown in Figure 1, possible solution structures of LiAlH₄ coordinated by bulky imine PhCH=NtBu (Im) and THF molecules are examined at first. Without coordinating THF molecules, LiAlH₄ should exist as imine-coordinated, double-hydride-bridged bimetal complexes of ImLiH₂AlH₂ and ImLiH₂AlH₃ that are nearly degenerate in free energy at room temperature, which should be favored in neat imine solution and under moderate heating, respectively. The separated ion pair of ImLi⁺ and AlH₃⁺ is 5.0 kcal/mol higher in free energy; further imine coordination to yield the cation ImLi⁺ is 3.3 kcal/mol endothermic and thus thermodynamically unfavorable even in neat imine solution. Triple-hydride-bridged structures found in gas-phase DFT optimization are unstable in solution and spontaneously optimized into double-hydride-bridged structures in our DFT calculations. With more coordinating THF molecules in solution, exergonic Im/THF ligand exchange and additional THF coordination at Lewis-acidic Li⁺ may occur easily via various neutral and/or ionic channels, eventually leading to the stable separated ion pair of Li(THF)⁺ and AlH₃⁻ in solution. Since bimetal LiHAl hydride and Li[N]Al amide bridges are crucial for the respective imine insertion and H₂ addition reaction steps (as shown below), stronger stabilization of Lewis-acidic Li⁺ with THF seems to be responsible for the relatively lower catalytic reactivity of LiAlH₄ observed in THF than in imine solutions.

As shown in Figure 2, starting from the double-imine-coordinated complex ImLiH₂AlH₄ intramolecular hydride to imine carbon transfer may occur via the six-membered-ring transition structure TS1 over a free energy barrier of 24.9 kcal/mol, which is −14.8 kcal/mol exergonic to form the hydride/amide doubly-bridged complex ImLi[N]HAlH₂. Further H₂ addition to the Li–N amide bond of ImLi[N]HAlH₂ is 4.7 kcal/mol endergonic over a barrier of 24.1 kcal/mol (via TS2) to form the desired amine product PhCH(NHtBuH)H[N] along with the initial ImLiH₂AlH₄ complex, formally completing the catalytic cycle of imine hydrogenation. Indeed, as the reverse reactions of metal amide hydrogenation, primary and secondary amines may react smoothly with LiAlH₄ to give aluminum amide products and H₂. In contrast, a high free energy barrier of 35.4 kcal/mol (via TS2a) is found for the H₂ addition to the terminal Al–N bond of ImLiH₂AlH[N] that is easily accessible from ImLi[N]HAlH₂ but 2.2 kcal/mol higher in free energy; a comparable high free barrier of ~37 kcal/mol was recently found for similar H₂ addition to Al–N bonds. The FLP-like H₂-activation over reactive ionic Li–N bonds found in this work is also consistent with our recent findings of reactive alkali metal species in the activation of small molecules such as CO and H₂. The new catalytic cycle involving ImLiH₂AlH₂ and ImLi[N]HAlH₃ as the respective imine and H₂ activator is −10.1 kcal/mol exergonic with an overall barrier of 24.9 kcal/mol, which should be efficient under moderate heating.

The actual situation is further complicated by potential imine insertion reactions of meta-stable ImLi[N]HAlH₂. As shown in Figure 2, upon additional imine coordination to ImLi[N]HAlH₂, hydride transfer from Al–H bonds to the carbon center of Li-bound imine C=N bonds may occur via easily accessible intermediate ImLiH₂AlH[N], which is −10.1 kcal/mol exergonic over a barrier of 23.8 kcal/mol (via TS3) to form the more stable complex ImLi[N]HAlH[N]. Consistent with recent experimental findings, the second imine insertion step is indeed kinetically 1.0 kcal/mol more favorable than the first one via TS1. Note that the imine insertion of ImLi[N]HAlH₂ (via TS3) is kinetically comparable with the competing H₂ addition (via TS2), but thermodynamically much more favorable. Since the final Gibbs free energies are computed for all species at 298 K and 1 mol/L.

Figure 1: DFT-computed Gibbs free energies (in kcal/mol at 298 K and 1 M concentration) of various solution structures of LiAlH₄ coordinated by imine PhCH=NtBu (Im) and THF molecules. Neutral and ionic complexes along with Lewis structures are connected by blue and black lines, respectively. Selected bond lengths are given in Å for the stable ImLiH₂AlH₂ contact ion pair.
Figure 2. DFT-computed Gibbs free energy paths (in kcal/mol at 298 K and 1 M concentration) of LiAlH₄ catalyzed hydrogenation of imine PhCH=NtBu (Im) with H₂. The imine insertion paths are shown in black lines while the H₂ activation paths are shown in red. For typical transition structures, both Lewis structures and ball-and-stick models are shown with most hydrogen atoms omitted for clarity and with selected bond lengths given in Å. Amine group [N=N(Bu)CH₂Ph].

As shown in Figure 2, the meta-stable hydride/amide bridged complex ImLi[N][HAlH[N] can still be involved in further imine insertion and H₂ activation steps. Again, direct H₂ addition over the Li–N amide bond of ImLi[N][HAlH[N] is 2.5 kcal/mol endergonic over a free energy barrier of 22.7 kcal/mol (via TS4) to form the amine product H[N] along with the complex ImLi[H][AlH[N]). The imine insertion paths are shown in black lines while the H₂ activation paths are shown in red. For typical transition structures, both Lewis structures and ball-and-stick models are shown with most hydrogen atoms omitted for clarity and with selected bond lengths given in Å. Amine group [N=N(Bu)CH₂Ph].

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Similarly, the double-hydride-bridged complex ImLi[H][AlH[N]) is also easily accessible from ImLi[N][HAlH[N] but is 1.5 kcal/mol less stable than ImLi[N][AlH₂] in solution. Starting from stable ImLi[N][AlH₂], further imine insertion via ImLi[H][AlH[N]) is −7.3 kcal/mol exergonic but over a high free energy barrier of 27.4 kcal/mol (via TS5) to form the complex ImLi[N][HAl[N] that is consistent with the long heating time required in experiment[8–9] to realize the slow third imine insertion that is unlikely to be important in an efficient catalytic imine hydrogenation. According to our DFT calculations, the Li–N amide bonds of ImLi[N][AlH₂] can also be directly involved in H₂ activation, which is however kinetically 1.0 kcal/mol less efficient than that via less stable ImLi[N][HAlH[N] (see ESI, TS3a). After the third imine insertion, further H₂ addition over the Li–N amide bond of ImLi[N][HAl[N]) is however prevented by an even higher barrier of 33.3 kcal/mol, likely due to steric hindrance (see ESI, TS6).

Interestingly, the cyclic complex ImLi[N][Alc (formally resulted from ImLi[N][AlH₂, via dehydrogenative ortho-phenyl metallaion with two endocyclic Al–C bonds) was found to be unreactive with H₂. Our DFT calculation show that the H₂ addition to a Li–N bond of ImLi[N][Alc is 15.4 kcal/mol endergonic over a moderate barrier of 22.9 kcal/mol (see ESI, TS7), which may cause facile H-isotope exchange at phenyl ortho sites due to kinetically more favorable H₂-release to regenerate the reactive Li–N bond. In contrast, the endocyclic Al–C bond of ImLi[N][Alc are shown to be even more stable than Al–N bonds towards H₂-addition (see ESI, TS8 vs. TS2a). In this sense, the double-amide-bridged complex ImLi[N][AlH₂ acts actually as a kinetic trap during the catalysis, with its slow hydrogenation with H₂ being crucial to recover the hydride/amide bridged bimetal species ImLi[N][HAlH[N] as an actual catalyst.

In conclusion, extensive state-of-the-art DFT calculations for LiAlH₄-catalyzed imine PhCH=NtBu (Im) hydrogenation in solution clearly show that hydride/amide bridged Li/Al species serve as active bimetal catalysts for imine hydrogenation with H₂, with the combinations of Lewis-acidic Li⁺ and Lewis-basic hydride and amide groups acting as FLP-like active sites for
Imine insertion and heterolytic H₂ activation, respectively. The Li/Al bimetal complexes resulted from the first and the second imine insertions of LiAlH₄ are the actual catalyst and the kinetic trap, respectively, with relatively slow catalyst recovery via H₂ addition. In contrast to recent proposal with Al–N amide bonds for H₂ activation, ionic Li–N amide bonds are much more reactive thus may represent a useful structural feature for active hydrogenation catalysts.

Computational Methods

All DFT calculations are performed with the TURBOMOLE 7.4 suite of programs.[14,16] The structures are fully optimized at the TPSS-D3/def2-TZVP + COSMO (THF) level, which combines the TPSS meta-GGA density functional[17] with the BJ-damped DFT-D3 dispersion correction[18] and the def2-TZVP basis set,[19] using the conductor-like Screening Model (COSMO)[18] for THF solvent (dielectric constant ε = 7.58 and diameter R_{solv} = 3.18 Å). The density-fitting R-J approach[20] is used to accelerate the calculations. The optimized structures are characterized by frequency analysis (no imaginary frequency for true minima and only one imaginary frequency for transition states) to provide thermal free-energy corrections (at 298.15 K and 1 atm) according to the modified ideal gas-rigid rotor-harmonic oscillator model.[21]

More accurate solution free energies in THF are computed with the COSMO-RS model[22] (parameter file: BP_TZVP_C30_1601.ctd) using the COSMOtherm package[23] based on the TPSS-D3 optimized structures, corrected by +1.89 kcal/mol to account for the 1 mol/L reference concentration in solution. To check the effects of the chosen DFT functional on the reaction energies and barriers, single-point calculations at both TPSS-D3[16] and hybrid-meta-GGA PW6B95-D3[24] levels are performed using the larger def2-QZVP[25] basis set. The final free energies are determined from the electronic single-point energies plus TPSS-D3 thermal corrections and COSMO-RS solution free energies. As also noted previously,[26] the overall results from both DFT methods are in good mutual agreement (−0.2 ± 1.5 kcal/mol, mean ± standard deviation for all relative energies) though as expected 2.1 ± 0.7 kcal/mol higher reaction barriers are found at the PW6B95-D3 level. In our discussion, the more reliable PW6B95-D3 + COSMO-RS free energies (in kcal/mol, at 298.15 K and 1 mol/L concentration) are used unless specified otherwise. The applied DFT methods in combination with the large AO basis set provide usually accurate electronic energies leading to errors for reaction energies (including barriers) on the order of typically 1–2 kcal/mol and even better for relative barrier differences between similar reactions due to error cancellation. This has been tested thoroughly for the huge data base GMTKN52[27] which is the common standard in the field of DFT benchmarking.

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Conflict of Interest

The authors declare no conflict of interest.

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