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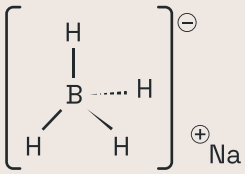
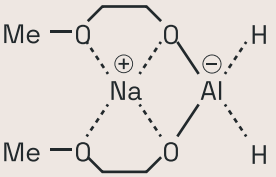
/COMPARATIVE ANALYSIS OF SODIUM BOROHYDRIDE AND SYNHYDRID®

COMPARATIVE ANALYSIS OF SODIUM BOROHYDRIDE AND SYNHYDRID®: REVISITING REACTIVITY, STABILITY, AND SOLUBILITY

Chemical reduction is a fundamental organic synthesis process that involves various functional groups. Noteworthy examples include converting carbonyl compounds (aldehydes, ketones, esters) to alcohols, nitriles and amides into amines and unsaturated carbon bonds to their saturated counterparts.

Among the frequently employed metal hydride-reducing agents are **Synhydrid® (sodium bis(2-methoxyethoxy) aluminumhydride)** and **sodium Borohydride ($NaBH_4$).**

CHEMICAL NAME	Sodium Borohydride	Sodium bis(2-methoxyethoxy) aluminium hydride
CHEMICAL FORMULA	$NaBH_4$	$NaAlH_2(OCH_2CH_2OCH_3)_2$
MOLECULAR STRUCTURE		
CAS NUMBER	16940-66-2	22722-98-1
MOLECULAR WEIGHT	37.83	202.16
FORM SUPPLIED BY CHEMATEK SPA	- White Crystalline Powder or White Granular (>98.0% purity) - 12% wt solution in aq. NaOH	Clear liquid sold as 70% wt minimum in toluene

/COMPARING METAL HYDRIDE AGENTS

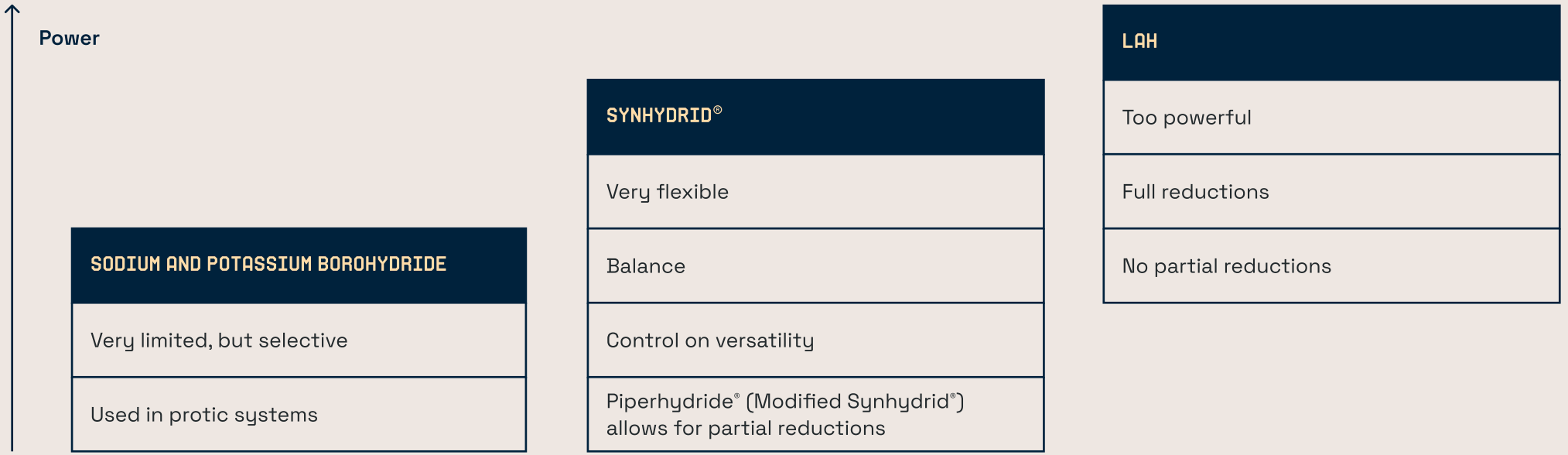
ADDRESSING THE CHARACTERISTICS OF LAH AND SODIUM & POTASSIUM BOROHYDRIDE

Lithium Aluminium Hydride (LAH) is renowned as a potent reducing agent in organic chemistry. It facilitates the reduction of diverse functional groups, including, for example, carbonyl compounds, epoxides, and nitriles.

However, its high reactivity limits its utility to complete reductions and poses considerable safety risks due to its propensity for violent reactions with water, moisture, and protic solvents. In contrast, sodium and potassium Borohydrides offer milder reactivity but are primarily suited for specific reductions, chiefly aldehydes and ketones.

Addressing the shortcomings of both LAH and Sodium & Potassium Borohydrides, Synhydrid® emerges as a promising alternative. As a toluene solution with a high concentration of 70% wt., Synhydrid® exhibits superior chemoselectivity. It can be tailored to enable partial reductions across a spectrum of functional groups, enhancing its applicability in diverse synthetic contexts.

Notably, its inherent stability eliminates concerns of self-ignition upon exposure to moisture or aqueous environments, making Synhydrid® a safer alternative to LAH for handling.



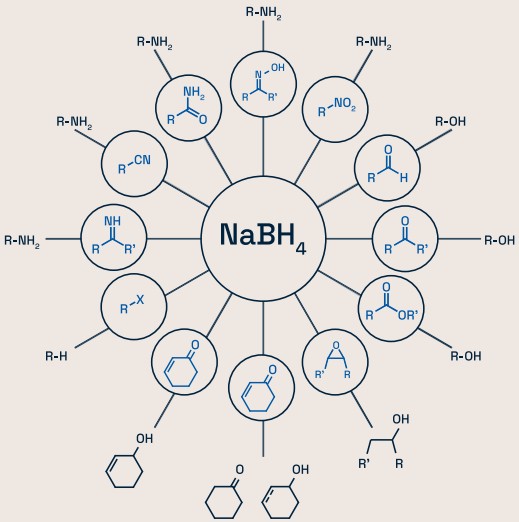
RELATIVITY AND SELECTIVITY

Sodium Borohydride is a milder reducing agent compared to Synhydrid®. Its primary application lies in reducing aldehydes and ketones into the corresponding alcohols. Notably, it exhibits remarkable chemoselectivity, affording the reduction of aldehydes even in the presence of ketones.
These reductions proceed by the formation of the sodium alkoxide followed by hydrolysis:

$$NaBH_4 + 4R_2C{=}O \longrightarrow NaB(O\text{-}CHR_2)_4$$

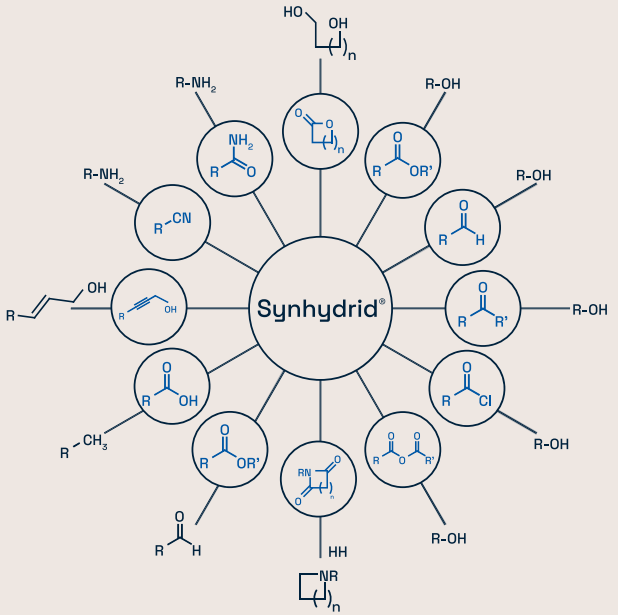
$$NaB(O\text{-}CHR_2)_4 + 4H_2O \longrightarrow 4HO\text{-}CHR_2 + NaOH + B(OH)_3$$

$NaBH_4$



Some interconversions require the use of a metal catalyst or additive

Synhydrid®



However, the reactivity profile of sodium Borohydride can be enhanced using selected additives such as organic acids (RCO_2H) or inorganic Lewis acids (e.g. I_2, BF_3, $AlCl_3$, $CeCl_3$, $CoCl_2$). They modify its reactivity to facilitate selective reactions of less reactive functional groups, e.g., esters, thereby expanding the scope of $NaBH_4$-mediated transformations.

The in situ reaction of $NaBH_4$ with Lewis acid yields highly reactive species, such as diborane or alane. It is important to emphasise that these products are highly flammable reducing agents. For instance, the formation of B_2H_6 occurs in the reaction of $NaBH_4$ with I_2 or BF_3, resulting in a highly flammable toxic reagent that liberates a significant amount of hydrogen (H_2) upon contact with water. Similarly, when $NaBH_4$ reacts with $AlCl_3$, alane (AlH_3) is produced, a compound notorious for its violent reactivity upon exposure to air and moisture.

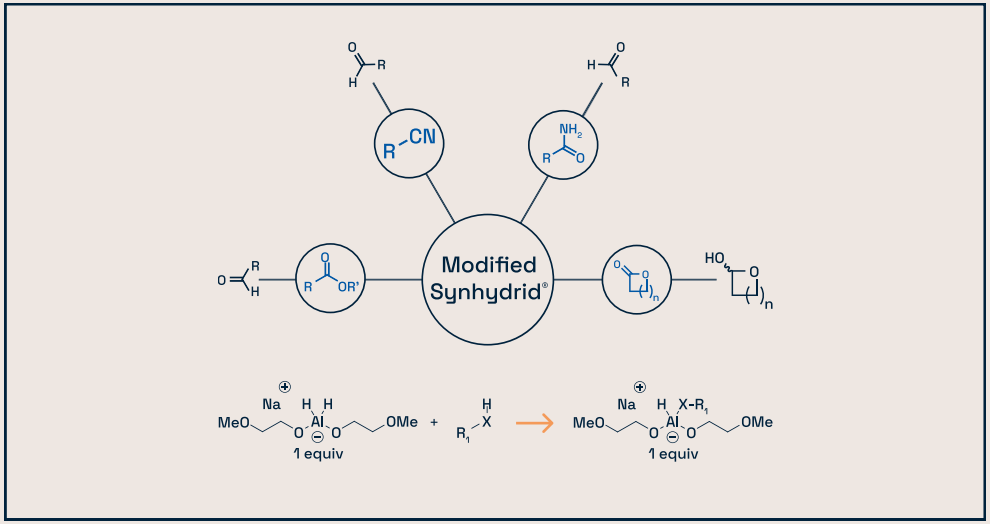
In contrast, Synhydrid® is a very capable reducing agent, adept at reducing a broader spectrum of functional groups, avoiding any concern of self-ignition. From epoxides to aldehydes, ketones, acyl halides and anhydrides, carboxylic acids, and esters, Synhydrid® exhibits exceptional efficacy in reducing them to the corresponding alcohols.

Notably, its reactivity extends to nitrogen derivates such as amides, nitriles, imides, and imines, converted into the corresponding amines. The reaction conditions can also be finely tuned to facilitate the reduction of carboxyl esters, amides, and nitriles to the aldehyde intermediates. Synhydrid® demonstrates greater selectivity than $LiAlH_4$ but less than $NaBH_4$, respecting its intermediate reactivity between these two reducing agents.

Nevertheless, Synhydrid® enables precise control over reduction reactions while minimising interference with other functional groups.

$$3NaBH_4 + 4\,AlCl_3 \longrightarrow 4AlH_3 + 3NaBCl_4$$

$$2AlH_3 + 6H_2O \longrightarrow 2Al(OH)_3 + 3H_2$$



PIPERHYDRIDE

c)

Reduction of different functional groups by Modified Synhydrid®. B and c) Modification of Synhydrid® with ligands of choice. Chematek is selling Modified Synhydrid®, which contains N-methylpiperazine as a ligand, Piperhydride®.

Building on the robust foundation of Synhydrid®, the introduction of Piperhydride®, a tailored modification featuring an amine ligand, starts a new era in nuanced reduction chemistry. As a ready-made alternative to DIBAL (diisobutylaluminium hydride), Piperhydride® offers precise control for partial reduction reactions.

Importantly, Piperhydride® finds its niche in reducing carboxylic esters, nitriles, and amides to aldehydes while facilitating conversion of lactones into lactols. The enhanced selectivity and versatility position Piperhydride® as a cornerstone in modern organic synthesis, able to offer transformative potential in pursuing complex molecules.

THERMAL STABILITY

- Sodium Borohydride is a white crystalline substance commonly sold in powder or pellet form.
- Its thermal stability is notable, with decomposition occurring above 400°C under vacuum conditions.
- The stability of $NaBH_4$ is subject to variations influenced by impurity levels, moisture exposure, and the heating rate.
- Synhydrid® demonstrates stability to temperatures up to 170°C, with decomposition occurring gradually up to 214°C but becoming spontaneous beyond this threshold.
- Investigations into the flash point of Synhydrid® have indicated a temperature of 150°C.

Sodium Borohydride is used in many applications including AgroChemicals, Pharmaceutical & Industrial.

SOLUBILITY AND REACTION CONDITIONS

Understanding the solubility of $NaBH_4$ across different solvents is crucial for its effective utilisation in diverse chemical processes. In water, $NaBH_4$ demonstrates significant solubility (55.0g/100g of water at 25°C), albeit with gradual hydrolysis over time. This results in the formation of sodium metaborate ($NaBO_2$) and the release of hydrogen gas. The extent of decomposition increases at higher temperatures or lower pH conditions.

$$NaBH_4 + 2H_2O \longrightarrow NaBO_2 + 4H_2$$

Sodium Borohydride is soluble in protic solvents, such as MeOH (13g/100mL) and EtOH (3.16g/100mL), despite also, in this case, decomposition to borates occurs over time.

Adding a base in the reaction conditions can mitigate this inherent instability. Sodium Borohydride exhibits stability and solubility in i-PrOH (0.37g/100mL) and diglyme (5.15g/100mL) while exhibiting extremely low ether solubility.

Additionally, it demonstrates solubility in ammonia (104g/100mL) and various amines, such as methylamine or ethylene diamine.

Given the solubility profile of Sodium Borohydride, its reactions are typically conducted under mild conditions, often using polar alcoholic solvents such as methanol or ethanol, as well as water.

In contrast, Synhydrid® exhibits insolubility in aliphatic and acyclic hydrocarbons, yet it boasts high solubility in ethers and aromatic hydrocarbons. Notably, the solubility is practically unlimited in aromatic hydrocarbons.

Notably, the solubility is practically unlimited in aromatic hydrocarbons like benzene and toluene and certain ethers such as THF and 1,2-dimethoxyethane.

As a result, it is common for Synhydrid® to conduct reactions in aromatics solvents (e.g., xylene, toluene) and ethers (e.g., methyl tert-butyl ether, tetrahydrofuran).

As mentioned, Synhydrid® doesn't self-ignite when exposed to moisture but remains sensitive to the hydrolysis of air and moisture, potentially leading to the release of hydrogen gas.

The hydrolysis product, $NaAlO(OCH_2CH_2OCH_3)_2$, is soluble in toluene. It is essential to note that Synhydrid® solutions remain clear even when partially hydrolysed occurs, a factor that can significantly impact the reproducibility of experimental data. Therefore, handling under an inert atmosphere is usually recommended.

$$NaAlH_2(OCH_2CH_2OCH_3)_2 + H_2O \rightarrow NaAlO(OCH_2CH_2OCH_3)_2 + 2H_2$$

The addition of Synhydrid® is typically through one of two principle procedures: the standard procedure involves adding the compound to a solution of Synhydrid®; the alternative procedure entails adding Synhydrid® to a solution containing the compound to be reduced. The appropriate procedure selection is contingent on factors such as the molecular complexity, the desired target, and the presence of other sensitive functional groups.

Versatile Applications of Synhydrid®: Going Beyond Reduction Chemistry

Synhydrid® is an effective dehydrating reagent for removing water from organic solvents, particularly in the dehydration of solvents employed in Grignard reactions. Additionally, its capability to activate the surface of Mg^0 by reducing the oxide coating renders Synhydrid® a reagent of choice for initiating Grignard reactions.

Synhydrid® also finds application in polymerisation technologies, demonstrating the capability to initiate anionic polymerisation of lactams and unsaturated monomers.

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